Zur Kasse

Notice of Opposition to a European Patent

To the European Patent Office

Tabulation marks

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I. Patent opposed

Opp. No. OPPO (1)

Patent No. EP 1 141 274

Application No. 00902354.0

Date of mention of the grant in the European Patent Bulletin (Art. 97(4), 99(1) EPC) 10 September 2003

Title of the invention:
Soluble Receptor BR43X2 and Methods of Using them for Therapy

II. Proprietor of the Patent Zymogenetics Inc.

first named in the patent specification

Opponent's or representative's reference (max. 15 spaces) 292/Q/085050007 OREF

III. Opponent OPPO (2)

Name / Address:
Human Genome Sciences Inc.
14200 Shady Grove Road
Rockville
MD 20850-7464
United States of America

State of residence or of principal place of business: United States of America

Telephone/Telex/Fax: +1 301 3098504 | +1 301 3098512

Multiple opponents: ☐ further opponents see additional sheet

IV. Authorisation OPPO (9)

1. Representative (Name only one representative to whom notification is to be made)

Name: Dr. Penny Gilbert

Address of place of business:
Bristows
3 Lincoln's Inn Fields
London WC2A 3AA
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Additional representative(s): ☐ (on additional sheet/see authorisation) OPPO (5)

2. Employee(s) of the opponent authorised for these opposition proceedings under Art. 133(3) EPC

Name(s):

Authorisation(s)

To 1./2.

☐ not considered necessary

☐ has/have been registered under No.

☒ is/are enclosed

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V. Opposition is filed against

— the patent as a whole [X]

— claim(s) No(s).

VI. Grounds for opposition:

Opposition is based on the following grounds:

(a) the subject-matter of the European patent opposed is not patentable (Art. 100(a) EPC) because:

— it is not new (Art. 52(1); 54 EPC) [X]

— it does not involve an inventive step (Art. 52(1); 56 EPC) [X]

— patentability is excluded on other grounds, i. e. Art. [ ]

(b) the patent opposed does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Art. 100(b) EPC; see Art. 83 EPC). [X]

(c) the subject-matter of the patent opposed extends beyond the content of the application/ of the earlier application as filed (Art. 100(c) EPC, see Art. 123(2) EPC). [ ]

VII. Facts and arguments

(Rule 55(c) EPC)
presented in support of the opposition are submitted herewith on a separate sheet (annex 1) [X]

VIII. Other requests:

If the Opposition Division envisages any decision other than revoking the Opposed Patent in its entirety, Oral Proceedings are requested.

IX. Evidence presented

Enclosed ☐

will be filed at a later date ☐

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Publication date

A. **Publications:**

1 The Publications set out in the attached statements of facts and arguments.

Particular relevance (page, column, line, fig.):

2

Particular relevance (page, column, line, fig.):

3

Particular relevance (page, column, line, fig.):

4

Particular relevance (page, column, line, fig.):

5

Particular relevance (page, column, line, fig.):

6

Particular relevance (page, column, line, fig.):

7

Particular relevance (page, column, line, fig.):

Continued on additional sheet ☐

B. **Other evidence**

Continued on additional sheet ☐

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X. Payment of the opposition fee is made

[X] as indicated in the enclosed voucher for payment of fees and costs (EPO Form 1010)

[ ]

XI. List of documents

Enclosure No.		No. of copies	
0	[X] Form for notice of opposition	2 (min. 2)	
1	[X] Facts and arguments (see VII.)	2 (min. 2)	
2	Copies of documents presented as evidence (see IX.)		
2a	[X] — Publications	2 (min. 2 of each)	
2b	[ ] — Other documents	(min. 2 of each)	
3	[X] Signed authorisation(s) (see IV.)	1	
4	[X] Voucher for payment of fees and costs (see X.)	1	
5	[ ] Cheque		
6	[ ] Additional sheet(s)	(min. 2 of each)	
7	[ ] Other (please specify here):		

XII. Signature of opponent or representative

Place Bristows, 3 Lincoln's Inn Fields, London WC2A 3AA, United Kingdom

Date 7 June 2004

Penny Gilbert

Dr. Penny Gilbert, Partner, Bristows

Please type name under signature. In the case of legal persons, the position which the person signing holds within the company should also be typed.

Our ref: 292/Q/08505 0007

Your ref:

7 June 2004

European Patent Office
Directorate General 2
Erhardtstrasse
D-80331
Munich
Germany

BY FAX - 0049 89 23 99 4465
CONFIRMATION BY COURIER

Dear Sirs

RE: European Patent No. 1 141 274
European Patent Application No. 00902354.0
Proprietors: ZymoGenetics, Inc.
Opponent: Human Genome Sciences, Inc.

On behalf of Human Genome Sciences, Inc. (HGS), 14200 Shady Grove Road, Rockville, MD 20850-7464, USA we are lodging an Opposition according to Article 99 EPC against EP 1 141 274 ("the Opposed Patent") in its entirety. The necessary fee has been paid today.

We oppose the Opposed Patent under Article 100(a) EPC, specifically in that it is not a patentable invention, lacks novelty and inventive step and does not satisfy Articles 52, 54 and 56 EPC. The Opposed Patent is further opposed under Article 100(b) EPC, in that it does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

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A. Detailed Statement of the Grounds of Opposition

1. The Opposition Brief refers to the documents listed below:

D1 WO 98/39361 (St. Jude Children's Research Hospital)

D2 "NF-AT Activation Induced by a CAML-Interacting Member of the Tumor Necrosis Factor Receptor Superfamily", Science, 1997, Vol. 278, pp. 138-141 (von Bulow et al.)

D3 "The BCMA gene, preferentially expressed during B lymphoid maturation, is bidirectionally transcribed", Nucleic Acids Research, 1994, Vol. 22, No. 7, pp. 1147-1154 (Laabi et al.)

D4 "BCMAp: an integral membrane protein in the Golgi apparatus of human mature B lymphocytes", International Immunology, 1995, Vol. 7, No. 7, pp. 1093-1106 (Gras et al.)

D5 "The characterization of murine BCMA gene defines it as a new member of the tumor necrosis factor receptor superfamily", International Immunology, 1998, Vol. 10, No. 11, pp. 1693-1702 (Madry et al.)

D6 WO 98/18921 (Human Genome Sciences, Inc.)

D7 EP 0 869 180 A1 (SmithKline Beecham Corp.)

D8 WO 98/55620 (Regeneron Pharmaceuticals, Inc.)

D9 "BAFF, a Novel Ligand of the Tumour Necrosis Factor Family, Stimulates B Cell Growth" J. Exp. Med., Vol. 189, No. 11, 7 June 1999, pp. 1747-1756 (Schneider et al.)

D10 "Mice Transgenic for BAFF Develop Lymphocytic Disorders Along with Autoimmune Manifestations" J. Exp. Med., Vol. 190, No. 11, 6 December 1999, pp. 1697-1710 (Mackay et al.)

D11 BLyS: Member of the Tumour Necrosis Factor Family and B Lymphocyte Stimulator" Science, Vol. 285, 9 July 1999, pp. 260-263 (Moore et al.)

D12 US application 09/302,863 (Immunex Corp.)

D13 US application 60/149,378 (Biogen, Inc.)

D14 US application 60/143,228 (Biogen, Inc.)

D15 US application 09/255,794 (Human Genome Sciences, Inc.)

D16 US application 60/119,906 (Amgen, Inc.)

D17 US application 60/166,271 (Amgen, Inc.)

D18 US application 09/226,533 (ZymoGenetics, Inc.)

B. Background

(a) The TNF Superfamily

2. The tumour necrosis factor ("TNF") superfamilies of ligands and receptors are a broad group of pleiotropic cytokine proteins involved in the regulation of cell proliferation, activation, differentiation and death. The TNF superfamily ligands are either type II transmembrane cytokine proteins, where the C-terminus of the protein is located extracellularly, or soluble proteins. The extracellular domains of TNF superfamily ligands contain a conserved region of around 150 amino acids comprising β-strands, while the remaining portions of the protein share little sequence homology. Many of the TNF ligand family members associate to form non-covalently bound trimeric structures (homotrimers).

3. The TNF ligands each bind to specific TNF receptors. The TNF receptors are transmembrane glycoproteins in which the N-terminus of the protein is located extracellularly, or soluble proteins. The extracellular domains of TNF receptors contain one or more characteristic cysteine-rich motifs (referred to as "pseudo repeats") which bind the TNF ligands. Like the TNF ligands, the TNF receptors usually form trimeric or multimeric non-covalent complexes.

(b) ztnf4 and its Receptors

4. ztnf4 is a TNF ligand which is able to stimulate the immune system. 'ztnf4 was first identified by the Opponent (see below) and is now known in the

art as TNFSF13B according to the terminology established by the Human Genome Organisation Nomenclature Committee. However, ztnf4 has also been referred to as BLyS (Human B Lymphocyte Stimulator), BAFF (B Cell Activating Factor belonging to the TNF Family), THANK, TALL-1, Kay Ligand and Neutrokine-alpha. In this Notice of Opposition we shall use the term "ztnf4" since that term is used in the Opposed Patent.

5. ztnf4 selectively binds to B lymphocytes, cells of the immune system that produce immunoglobulin (also referred to herein as antibody). ztnf4 has been shown to bind three TNF receptors which are located on B cells: TNFRSF13B, TNFRSF13C and TNFRSF17. These TNF receptors have also been referred to in the art as TACI, BAFF Receptor, and BCMA, respectively. The Opposed Patent concerns TNFRSF13B, TNFRSF17 and an isoform (i.e., a splice variant) of TNFRSF13B. It refers to these receptors as TACI, BCMA and BR43x2, respectively, and those terms are adopted in this Notice of Opposition. TACI is a TNF receptor with two conserved cysteine–rich pseudo repeats whilst BCMA and BR43x2 each have a single cysteine–rich pseudo repeat. These regions of the extracellular domains of the receptors are involved in binding ztnf4.

6. BR43x2 is an isoform of TACI in which a region of the TACI sequence from amino acid residue 21 to residue 67 which contains the first cysteine-rich pseudo repeat of TACI has been replaced by a single tryptophan residue. BR43x2 is therefore a 247 amino acid protein the sequence of which is identical to that of TACI except in that respect. The second cysteine-rich pseudo repeat of TACI (amino acid residues 70 to 104 of TACI) is present in BR43x2. BR43x2 was produced by the Patentee by expression cloning from an activated B cell line cDNA library as described in Example 1 of the Opposed Patent.

7. In the body, ztnf4, in combination with its receptors, stimulates B cell growth and differentiation. Immature B cells are produced in the bone marrow and differentiate into mature, resting B cells as they migrate to the

spleen and lymph nodes. Upon activation by antigen, mature B cells proliferate and differentiate further into antibody secreting B cells known as plasma cells. ztnf4 functions in conjunction with its receptors to stimulate B cell proliferation and differentiation at both the immature-to-mature and the mature-to-plasma B cell transitions. This process is all part of the immune system's natural hematopoietic cell development.

8. Due to their biological functions of effecting B cell growth, proliferation and differentiation, ztnf4, its receptors and related molecules have a number of useful therapeutic functions. ztnf4 and similar molecules can be used to treat immune disorders associated with too little antibody production because they have the ability to stimulate the immune system. Two such disorders which may be treated in this way are Common Variable Immunodeficiency and Immunoglobulin A deficiency.

9. Alternatively, antagonists of ztnf4 activity, such as antibodies specific to ztnf4 and antibodies specific to its receptors, and the receptors themselves and similar molecules can be used to treat disorders associated with too much or inappropriate antibody production. Autoimmune conditions, for example, arise when the body's immune system fails to distinguish between the body's own cells and tissues and those of foreign pathogens, resulting in an immune response that attacks the body itself. Elevated levels of ztnf4 have been found in the serum of patients with autoimmune diseases which are characterized by the production of autoantibodies, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Therefore treatment of SLE and RA patients with ztnf4 antagonists, such as monoclonal antibodies which bind to ztnf4 and similar molecules, is currently being studied.

10. A third way in which ztnf4, its receptors and related molecules can be used to treat disease is by utilizing their common property of binding specifically to B cells. For instance, certain types of cancers, such as Hodgkin's lymphoma, multiple myeloma and chronic lymphocytic

leukaemia, originate from unregulated and malignant growth of B cells. Drugs which link ztnf4 to a toxin or to a source of radiation capable of killing malignant B cells could prove effective for treating these conditions and are currently being studied.

(c) *Research and Filing History*

11. Multiple research groups have been active in the characterization of ztnf4 and its receptors. This is demonstrated by the number of patent applications filed and papers published in this field. A timeline listing a selection of relevant patent filings and publications and the groups involved forms Annex A.

12. On 3 March 1998, St. Jude Children's Research Hospital filed a PCT application (PCT/US98/04270) disclosing the amino acid sequence of TACI as well as a polynucleotide sequence encoding TACI, and providing details of its function and therapeutic applications. This application, which claimed priority from US application serial no. 08/810,572 filed on 3 March 1997, published as WO 98/39361 (**D1** below) on 11 September 1998. The named inventors of **D1** had also published a paper in 1997 (**D2**) disclosing TACI. Immunex Corporation also filed patent applications describing TACI and methods of use of TACI. Immunex filed US patent application 09/302,863 (**D12**) on 30 April 1999, after the claimed priority date of the Opposed Patent but before its filing date. This application was used to claim priority for PCT application PCT/US00/10282 which was filed on 14 April 2000 and published as WO 00/67034 on 9 November 2000. WO 00/67034 later entered the European phase as European Patent application no. 00922273.8.

13. The amino acid sequence of BCMA and encoding polynucleotide sequences were published in the 1990s by research groups in France. These publications include **D3**, **D4** and **D5**, published in 1994. 1995 and 1998, respectively, referred to further below. Biogen Inc. also filed patent

applications describing BCMA and methods of use of BCMA. Biogen Inc. filed US patent application 60/149,378 (**D13**) on 17 August 1999, after the claimed priority date of the Opposed Patent but before its filing date. This application (amongst others) was used to claim priority for PCT application PCT/US00/22507 which was filed on 16 August 2000 and published as WO 01/12812 on 22 February 2001. WO 01/12812 later entered the European phase as European Patent application no. 00957502.8.

14. Earlier, on 25 October 1996 the Opponent had filed the first application in relation to ztnf4, identifying the full-length ztnf4 protein (initially referred to as "Neutrokine-alpha"), its function and therapeutic applications. This application published as WO 98/18921 (**D6** below) on 7 May 1998. SmithKline Beecham Corp. filed US application serial nos. 60/041,797 and 08/984,396 concerning ztnf4 (referred to as "TL-5") on 2 April 1997 and 3 December 1997, respectively. It subsequently filed a European application, claiming priority from those applications, on 1 April 1998 which published on 7 October 1998 as EP 0 869 180 A1 (**D7** below). This application included a sequence for ztnf4 and described its therapeutic applications. Additionally, Regeneron Pharmaceuticals, Inc. filed US patent applications 60/048,776 and 60/066,386 relating to ztnf4 on 6 June 1997 and 21 November 1997, respectively. These were used to claim priority on its PCT application PCT/US98/11153 filed on 3 June 1998 and which published as WO 98/55620 (**D8** below) on 10 December 1998. WO 98/55620 disclosed the N-terminally truncated fragment of ztnf4 referred to as the ztnf4 fragment below.

15. Several articles concerning ztnf4 and its biological properties were published in 1999, after the claimed priority date of the Opposed Patent but before its filing date (**D9**, **D10** and **D11** referred to below). Additionally, several US patent applications were filed after the claimed priority date of the Opposed Patent but before its filing date. These patent applications describe ztnf4 and methods of use of ztnf4. Biogen filed US patent application 60/143,228 (**D14**) on 9 July 1999. This application (along with

another US application) was used to claim priority for PCT application PCT/US00/01788 which was filed on 25 January 2000 and published as WO 00/43032 on 27 July 2000. WO 00/43032 later entered the European phase as European Patent application no. 00909970.6. Human Genome Sciences filed US patent application 09/255,794 (**D15**) on 23 February 1999. This application (along with a number of other US applications) was used to claim priority for PCT application PCT/US00/04336 which was filed on 22 February 2000 and published as WO 00/50597 on 31 August 2000. WO 00/50597 later entered the European phase as European Patent application no. 00908739.6.

16. Amgen filed US patent applications 60/119,906 (**D16**) and 60/166,271 (**D17**), both concerning ztnf4, on 12 February 1999 and 18 November 1999, respectively. These applications were used to claim priority for PCT application PCT/US00/03653 which was filed on 11 February 2000 and published as WO 00/47740 on 17 August 2000. WO 00/47740 later entered the European phase as European Patent application no. 00907280.2.

C. <u>The Opposed Patent</u>

17. The Opposed Patent is entitled "Soluble Receptor BR43x2 and Methods of using them for Therapy" and is owned by Zymogenetics Inc. It was filed on 7 January 2000 and claims priority from US patent application serial no. 09/226,533 (**D18**). The Opposed Patent was granted on 10 September 2003.

18. The Opposed Patent concerns ztnf4 and its receptors, TACI, BCMA and BR43x2 (an isoform of TACI as described above) which it reports were found to bind ztnf4. The Opposed Patent acknowledges that TACI and BCMA were known at the priority date and cites prior art in which their amino acid sequences were given (e.g. **D1** and **D4** referred to below which disclose TACI and BCMA respectively). It also acknowledges that ztnf4

had been previously identified (e.g. referring to prior art including **D6. D9** and **D11** described below). The invention is said to relate in part to the discovery of the DNA sequence and corresponding amino acid sequence of the isoform of TACI, BR43x2.

19. A total of 60 DNA and amino acid sequences are given in the patent of which SEQ ID NOS: 2, 4, 6, 8, 10, 18 and 20 are referred to in the claims. The Opposed Patent does not identify all of these sequences adequately and in some instances creates confusion by referring to the wrong SEQ ID NOS (as explained below). From carrying out its own analyses and reviewing the literature, the Opponent has identified the sequences referred to in the claims of the Opposed Patent as follows:

- SEQ ID NO:2 is the amino acid sequence of BR43x2;
- SEQ ID NO:4 is the amino acid sequence of the (soluble) extracellular domain of BR43x2;
- SEQ ID NO:6 is the amino acid sequence of human TACI;
- SEQ ID NO:8 is the amino acid sequence of human BCMA;
- SEQ ID NO:10 is the consensus cysteine-rich pseudo repeat shared by TACI, TACI splice variants and BCMA;
- SEQ ID NO:18 is a fragment containing amino acid residues 22 to 285 of human ztnf4 (omitting N-terminal residues 1-21 of the full sequence) which is referred to as the "ztnf4 fragment" below; and
- SEQ ID NO:20 is the amino acid sequence of murine TACI.

20. Far fewer sequences were provided in US application 09/226,533 (**D18**), from which the Opposed Patent claims priority. Hence the SEQ ID NOS used in **D18** are different to those used in the Opposed Patent in some instances. For ease of reference a list of the SEQ ID NOS that appear in the claims of the Opposed Patent alongside the corresponding SEQ ID NOS from the priority filing **D18** and details of what each pertains to is included in Annex B.

21. Broadly speaking, the claims of the Opposed Patent fall into 4 categories:

(i) "Swiss-style" claims covering TACI, BR43x2 and BCMA fragments, and the cysteine-rich pseudo repeat of SEQ ID NO:10; antibodies and antibody fragments that bind TACI, BCMA, BR43x2, BR43x2 fragments, the cysteine-rich pseudo repeat of SEQ ID NO:10 and the ztnf4 fragment; and related molecules (claims 1 to 3 and 13 to 28);

(ii) "Swiss-style" claims covering TACI, BCMA, and BR43x2 related fusion proteins (claims 4 to 12);

(iii) Claims concerning BR43x2 alone (claims 29 to 35); and

(iv) Pharmaceutical compositions comprising antibodies to TACI, BCMA, BR43x2, a BR43x2 fragment and the cysteine-rich pseudo repeat, SEQ ID NO:10 (claims 36 to 38).

22. Claims 1 to 3 are drafted in "Swiss style" and attempt to claim medical uses of compositions based on their previously reported, intrinsic biological activities. Claim 1 covers use of a compound selected from the following group in the manufacture of a medicament for inhibiting ztnf4 activity in a mammal:

a) a polypeptide comprising the extracellular domain of BR43x2 (SEQ ID NO:2);
b) a soluble polypeptide comprising the extracellular domain of TACI;
c) a polypeptide comprising the extracellular domain of BCMA;
d) a polypeptide comprising the sequence of SEQ ID NO:10;
e) an antibody or antibody fragment which specifically binds to a polypeptide of SEQ ID NO:2;
f) an antibody or antibody fragment which specifically binds to a polypeptide of SEQ ID NO:4;
g) an antibody or antibody fragment which specifically binds to a polypeptide of SEQ ID NO:6;

h) an antibody or antibody fragment which specifically binds to a polypeptide of SEQ ID NO:8;

i) an antibody or antibody fragment which specifically binds to a polypeptide of SEQ ID NO:10;

j) (Element j is omitted in the claim)

k) a polypeptide of SEQ ID NO:4;

l) amino acid residues 1-166 of SEQ ID NO:6;

m) amino acid residues 8-37 of SEQ ID NO:8; and

n) amino acid residues 1-48 of SEQ ID NO:8.

23. Claim 2 is dependent on claim 1 and covers uses of the same compositions for such inhibition where the mammal is a primate.

24. Claim 3 is an independent "Swiss style" claim covering use of a compound selected from the following group in the manufacture of a medicament for inhibiting BR43x2, TACI or BCMA receptor-ztnf4 engagement:

a) a polypeptide comprising the extracellular domain of BR43x2 (SEQ ID NO:2);

b) a soluble polypeptide comprising the extracellular domain of TACI;

c) a polypeptide comprising the extracellular domain of BCMA;

d) a polypeptide comprising the sequence of SEQ ID NO:10;

e) an antibody or antibody fragment which specifically binds to a polypeptide of SEQ ID NO:2;

f) an antibody or antibody fragment which specifically binds to a polypeptide of SEQ ID NO:4;

g) an antibody or antibody fragment which specifically binds to a polypeptide of SEQ ID NO:6;

h) an antibody or antibody fragment which specifically binds to a polypeptide of SEQ ID NO:8;

i) an antibody or antibody fragment which specifically binds to a polypeptide of SEQ ID NO:10;

j) an antibody or antibody fragment which specifically binds to a polypeptide of SEQ ID NO:18;

k) an antibody or antibody fragment which specifically binds to a polypeptide of SEQ ID NO:20;

l) a polypeptide of SEQ ID NO:4;

m) amino acid residues 1-166 of SEQ ID NO:6;

n) amino acid residues 8-37 of SEQ ID NO:8; and

o) amino acid residues 1-48 of SEQ ID NO:8.

The compositions covered by claim 3 therefore include antibodies or antibody fragments specific to SEQ ID NO:18 and SEQ ID NO:20 in addition to the compounds covered by claim 1.

25. Claims 4 to 12 are dependent on claims 1 to 3. They are drafted in "Swiss style" and attempt to claim the uses referred to above where the compounds in question are particular fusion proteins. Claim 4 covers such uses where the compound is a fusion protein consisting of a first and a second portion joined by a peptide bond, the first portion comprising a polypeptide selected from the following group:

a) a polypeptide comprising the sequence of SEQ ID NO:8;

b) a polypeptide comprising amino acid residues 25-58 of SEQ ID NO:2;

c) a polypeptide comprising amino acid residues 34-66 of SEQ ID NO:6;

d) a polypeptide comprising amino acid residues 71-104 of SEQ ID NO:6;

e) a polypeptide comprising amino acid residues 25-104 of SEQ ID NO:6;

f) a polypeptide comprising amino acid residues 8-37 of SEQ ID NO:8;

g) a polypeptide comprising amino acid residues 41-88 of SEQ ID NO:8;

h) a polypeptide comprising amino acid residues 8-88 of SEQ ID NO:8;

and the second portion comprising another polypeptide.

26. Claim 5 covers uses according to claim 4 where the first portion of the fusion protein comprises a polypeptide selected from the following group:

a) amino acid residues 59-120 of SEQ ID NO:2;
b) amino acid residues 105-166 of SEQ ID NO:6; and
c) amino acid residues 89-150 of SEQ ID NO:8.

27. Claim 6 covers uses according to claim 4 where the first portion of the fusion protein comprises a polypeptide selected from the following group:

a) a polypeptide comprising the extracellular domain of BR43x2 (SEQ ID NO:2);
b) a soluble polypeptide comprising the extracellular domain of TACI; and
c) a polypeptide comprising the extracellular domain of BCMA.

28. Claim 7 covers uses according to claim 4 where the first portion of the fusion protein comprises a polypeptide selected from the following group:

a) a polypeptide of SEQ ID NO:4;
b) amino acid residues 1-154 of SEQ ID NOS:6; and
c) amino acid residues 1-48 of SEQ ID NO:8.

29. Claims 8 to 12 are dependent on claims 4 to 7 and cover uses of fusion proteins which have an immunoglobulin heavy chain constant region component. Claim 8 covers uses according to claims 4 to 7 where this component forms the second portion of the fusion protein. Claim 9 covers uses according to claim 8 where the immunoglobulin heavy chain constant region component is a human immunoglobulin heavy chain constant region. Claim 10 covers uses according to claim 9 where the human immunoglobulin heavy chain constant region is human immunoglobulin heavy chain constant region of IgG1.

30. Claim 11 covers uses according to claims 8 to 10 where the medicament comprises a multimer of the fusion proteins, and claim 12 covers uses according to claim 11 where the medicament comprises an

immunoglobulin heavy chain constant region which contains two constant region domains and lacks the variable region.

31. Claims 13 to 28 are dependent on claims 1 to 12. They are drafted in "Swiss style" and attempt to claim the uses referred to above where the uses are directed at particular biological and therapeutic activities of TACI, BR43x2 , BCMA, and the cysteine-rich pseudo repeat of SEQ ID NO:10; antibodies that bind TACI, BCMA, BR43x2, the cysteine-rich pseudo repeat of SEQ ID NO:10 or ztnf4; as well as fragments of the aforementioned molecules and related molecules. Claim 13 covers uses according to claims 1 to 12 where the medicament is for treatment of B lymphocytes, and claims 14 and 15 cover uses according to claim 13 where the B lymphocytes are activated and resting respectively.

32. Claim 16 covers uses according to claims 1 to 15 where the medicament is for inhibiting antibody production, and claim 17 covers uses according to claim 16 where the antibody production is associated with an autoimmune disease. Claim 18 covers uses according to claim 17 where the autoimmune disease is SLE, myasthenia gravis, multiple sclerosis, or RA.

33. Claim 19 covers uses according to claims 1 to 18 for treatment of asthma, bronchitis, emphysema and end stage renal failure, and claim 20 covers uses according to claim 19 where the renal disease is glomerulonephritis, vasculitis, nephritis or pyelonephritis. Claim 21 covers uses according to claims 1 to 20 for treatment of renal neoplasms, multiple myelomas, lymphomas, light chain neuropathy or amyloidosis.

34. Claim 22 covers uses according to claims 1-21 for inhibiting effector T cells, and claims 23 and 24 cover uses according to claim 22 for moderating immune response and where the inhibition comprises immunosuppression respectively. Claim 25 covers uses according to claim 24 where the immunosuppression is associated with graft rejection, graft versus host disease, autoimmune disease or inflammation.

35. Claim 26 covers uses according to claim 17 referred to above where the autoimmune disease is insulin dependent diabetes mellitus or Crohn's Disease. Claim 27 covers uses according to claims 1 to 26 for treatment of inflammation, and claim 28 covers uses according to claim 27 where the inflammation is associated with joint pain, swelling, anemia or septic shock.

36. Claims 29 to 35 concern BR43x2 alone (rather than extending to TACI, BCMA and ztnf4). Claim 29 covers polynucleotides encoding SEQ ID NO:2 (BR43x2) and Claim 30 covers the specific isolated polynucleotide with SEQ ID NO:1 which is one such polynucleotide.

37. Claim 31 is directed at expression vectors for BR43x2 production and covers expression vectors comprising the following operably linked elements: a transcription promoter; a polynucleotide molecule according to claim 29; and, a transcription terminator. Claim 32 covers cultured cells into which an expression vector according to claim 31 has been introduced where the cultured cells express the encoded (BR43x2) polypeptide. Claim 33 covers a method of producing a polypeptide comprising culturing a cell into which an expression vector according to claim 31 has been introduced where the encoded polypeptide is expressed by the cell and recovered.

38. Claim 34 covers the isolated polypeptide of SEQ ID NO:2 (BR43x2), and claim 35 covers the polypeptide of claim 34 in combination with a pharmaceutically acceptable vehicle.

39. Claims 36 to 38 cover antibodies to TACI, BCMA, BR43x2 and the cysteine-rich pseudo repeat, SEQ ID NO:10. Claim 36 covers pharmaceutical compositions comprising a pharmaceutical carrier and antibodies or antibody fragments which specifically bind to a polypeptide of: SEQ ID NOS: 2, 4, 6, 8, or 10.

40. Claim 37 covers compositions according to claim 36 where the antibody or antibody fragment is selected from the following group:

a) polyclonal antibody;
b) murine monoclonal antibody;
c) humanized antibody derived from b); and
d) human monoclonal antibody.

41. Claim 38 covers compositions according to claims 36 and 37 where the antibody fragment is selected from the group consisting of F(ab'), Fab, Fv and scFv.

D. Patentability (Article 100(a) EPC)

(i) Methods for treatment of the human body (Article 52 (4))

42. As noted above, claims 1 to 28 of the Opposed Patent are formulated in "Swiss style" and are drafted in an attempt to claim medical uses because others had previously disclosed compositions containing TACI, BCMA, ztnf4 and related molecules and their uses (see below). The Boards of Appeal have accepted that in principle it is legitimate to allow claims directed to the use of a substance or composition for the manufacture of a medicament for a specified new and inventive therapeutic application (see for example G 5/83).

43. However, Claims 1 to 16 and 22 to 24 of the Opposed Patent are unacceptable as they are not directed to a therapeutic application. These claims merely recite intrinsic biological activities of anti-ztnf4 antibodies, TACI, BR43x2, BCMA and other ztnf4 receptors and related molecules, such as inhibiting ztnf4 activity, inhibiting receptor-ztnf4 engagement, treatment of B-lymphocytes, inhibiting antibody production and inhibiting effector T cells.

44. As enunciated in T 4/98, "Swiss style" claims can only be acceptable where they relate to the use of substances or compositions for the preparation of a medicament intended for use in a method referred to in Article 52(4), i.e., therapy. The Board defined the concept of "therapy" or "therapeutic application" as the treatment of a specific illness or disease with a specified chemical substance or composition in a specified human or animal subject in need of such treatment. It was determined that a mere process feature, such as an intrinsic biological activity, could not be contrived as specifying a particular method of treatment within the meaning of Article 52(4). Thus, T 4/98 confirms that medical use claims are only allowable as long as the substances or compositions of the claims are stated to be for use in a therapeutic application in accordance with Article 52(4).

45. Claims 1 to 16 and 22 to 24 of the Opposed Patent do not specify any illness or disease to be treated, instead they refer to intrinsic biological activities which are inherent properties of anti-ztnf4 antibodies, ztnf4 receptors and/or ztnf4 receptor antagonists. They are therefore not capable of being valid second (or first) medical use claims. Accordingly, the validity of claims 1 to 16 and 22 to 24 must be assessed without reference to Article 54(5). Prior disclosure of the substances recited in these claims and of the biological activities of these substances will therefore deprive these claims of novelty (see below).

(ii) Priority

46. As noted above, the priority claimed for the Opposed Patent is based on a US patent application filed on 7 January 1999 by Zymogenetics Inc. with serial no. 09/226,533 (**D18**). However, the scope of the invention(s) was broadened between **D18** and the claims of the Opposed Patent as granted. The Opposed Patent is not therefore entitled to the claimed priority date.

47. In particular, the Opposed Patent includes a far more extensive description of the immune system-related disorders that can be treated with the compounds of the invention(s) than **D18** (e.g. page 3 at lines 1 to 34 and page 14 line 40 to page 15 line 14 of the Opposed Patent) and many of the specific fragments referred to in the claims of the Opposed Patent were not mentioned at all in **D18**. In addition, SEQ ID NOS:18 and 20 (the amino acid sequences of the ztnf4 fragment and murine TACI respectively) were not included in **D18**. Moreover, antibodies and antibody fragments specific to either SEQ ID NO:18 or SEQ ID NO:20 which form part of claim 3 of the Opposed Patent (and its dependent claims), were also not included in **D18**. It is also notable that **D18** suggested that resting B lymphocytes would not be treated by the compounds of the invention (see for example page 51 at lines 9-10 of **D18**).

48. The skilled person would not have been able to derive the subject matter of at least claims 1, 3 to 7, 10 to 12, 15, 18 to 22, 25 to 28 and 36 (and their dependent claims) of the Opposed Patent directly and unambiguously, using common general knowledge, from **D18**. Hence for the purpose of those claims, **D18** does not disclose the same invention as the Opposed Patent (G 2/98). The Opposed Patent's claims for priority for at least claims 1, 3 to 7, 10 to 12, 15, 18 to 22, 25 to 28 and 36 (and their dependent claims) based on **D18** are therefore invalid, and the correct priority date that applies to those claims is the filing date, 7 January 2000. The validity of those claims must therefore be assessed at this later date (the "Later Priority Date"). To the extent that the Opposition Division finds, contrary to the Opponent's submission, that any of claims 1, 3 to 7, 10 to 12, 15, 18 to 22, 25 to 28 and 36 (and their dependent claims) of the Opposed Patent are entitled to the claimed priority date, the Later Priority Date should apply to the remainder of those claims.

(iii) Lack of novelty (Article 54 EPC) assessed at the Claimed Priority Date

49. As noted above, the Opponent submits that novelty should be assessed at the Later Priority Date for at least claims 1, 3 to 7, 10 to 12, 15, 18 to 22, 25 to 28 and 36 (and their dependent claims) of the Opposed Patent. The assessment of novelty in relation to the remaining claims and to any of claims 1, 3 to 7, 10 to 12, 15, 18 to 22, 25 to 28 and 36 (and their dependent claims) which, contrary to the Opponent's submission, the Opposition Division finds have valid priority will be made at the claimed priority date. **D1** to **D8** are available for novelty purposes at the claimed priority date.

D1 – WO 98/39361 (St. Jude Children's Research Hospital)

50. **D1** is an application in the name of St. Jude Children's Research Hospital. It was filed on 3 March 1998 and published on 11 September 1998. **D1** is therefore prior art under Articles 54(2) and 56 EPC and available as a reference for assessing both the novelty and inventive step of the alleged invention(s) claimed in the Opposed Patent. **D1** was cited in the Opposed Patent.

51. **D1** describes human TACI, a 293 amino acid protein (SEQ ID NO:2, pages 70-71), the amino acid sequence of which is 100% identical to the human TACI protein which is 'SEQ ID NO:6' in the Opposed Patent (page 40-41)[1]. **D1** therefore disclosed the full-length amino acid sequence of human TACI. It also disclosed a polynucleotide encoding TACI (SEQ ID NO:1, pages 69-70) and the location of the two cysteine-rich pseudo repeats in TACI (page 19 at lines 20-31). These regions, amino acid residues 33-66 and 70-104 of SEQ ID NO:2, both fall within the definition of SEQ ID

[1] There are some discrepancies in the Opposed Patent regarding the sequence number for the TACI sequence. For instance, page 3 at lines 52-53 suggests that SEQ ID NO:8 is TACI whilst page 6 at lines 49-50 suggests it is SEQ ID NO:6. However the amino acid sequence for SEQ ID NO:6 (pages 40-41) is that of human TACI.

NO:10 of the Opposed Patent (pages 45-47). Two sequences corresponding to SEQ ID NO:10 are therefore disclosed in **D1**.

52. **D1** contains a broad teaching, specifically disclosing the production of TACI, TACI fragments (including the extracellular N-terminal domain of TACI) and fusion proteins, production of TACI and TACI fragments using vectors, host cells and recombinant methods as well as describing screening methods for identifying agonists and antagonists of TACI activity (including antibodies specific for TACI and its fragments). Furthermore, **D1** describes methods for identifying the endogenous TACI ligand (now known to be ztnf4), methods of screening for immunosuppressant drugs that inhibit activation of B cells and therapeutic uses of TACI and related molecules in various disorders of the immune system.

53. As discussed above, claims 1 to 16 and 22 to 24 of the Opposed Patent are drafted in "Swiss style" and cover compositions which include the extracellular domain of TACI and a TACI fragment (amino acid residues 1-166 of SEQ ID NO:6), fusion proteins containing TACI and TACI fragments (e.g. residues 34-66 and 71-104 and 25-104 of SEQ ID NO:6 and the extracellular domain of TACI), antibodies and antibody fragments specific to TACI (SEQ ID NO:6), antibodies and antibody fragments specific to BR43x2 (SEQ ID NO:2) and to a BR43x2 fragment (SEQ ID NO:4) and antibodies and antibody fragments specific to murine TACI (SEQ ID NO:20). They also cover compositions comprising polypeptides of SEQ ID NO:10 (a consensus cysteine-rich pseudo repeat motif common to TACI, TACI splice variants and BCMA) and antibodies and antibody fragments specific to such polypeptides. However, they do not claim a therapeutic application (T 4/98) but rather they refer to intrinsic biological activities of TACI, and related substances. As these claims are not valid medical use claims, the prior disclosure of these relevant substances deprives these claims of novelty. Accordingly, the disclosure of the extracellular domain of TACI (e.g. page 6 at lines 22-25, page 7 at lines

20-24, page 18 at lines 24-30, page 56 at lines 1-3 and in SEQ ID NO:6 (p73) and claims 18 and 19), other TACI fragments (e.g. page 19 at lines 6-10), TACI fusion proteins (e.g. page 24 line 19 to page 25 line 28 where they are referred to as 'chimeric protcins'), antibodies and antibody fragments specific to TACI (e.g. page 9 at lines 5-10, page 49 line 21 to page 52 line 16 and claims 26 and 27), TACI genes from other species, preparation of TACI-specific antibodies in mice and their administration to mice (e.g. page 34 at lines 1-4, page 50 at lines 12-15 and page 60 at lines 6-13) and the sequences of the two cysteine-rich pseudo repeats in **D1** anticipates claims 1 to 16 and 22 to 24. Additionally because TACI and BR43x2 share long stretches of amino acids in common, many antibodies that specifically bind TACI, such as those disclosed in **D1**, are likely to also bind BR43x2 and BR43x2 fragments.

54. Moreover, even if these biologically defined claims were acceptable as proper medical use claims, they would still lack novelty based on **D1**. For example, **D1** discloses that TACI is a cell surface receptor normally present on B-lymphocytes and to a lesser extent on immature T-lymphocytes which participates in alternate or co-stimulatory pathways to activate or control lymphocyte development and function, including the response of lymphocytes to foreign antigens (page 15 at lines 19-29). The role of TACI in binding its endogenous ligand (now known to be ztnf4) is disclosed in **D1** along with means of identifying the ligand and a description of its likely functions (e.g. page 10 line 3 to page 11 line 14 and page 52 line 18 to page 54 line 10). **D1** also discloses the use of TACI related molecules including the claimed TACI substances for inhibiting TACI activity (e.g. page 58 at lines 1-6) and the administration of such substances to mammals and preferably humans (e.g. page 60 at lines 4-13). Claims 1 to 12 are therefore anticipated. To the extent that any aspect of these claims is not disclosed by **D1**, these claims lack inventive step over **D1** (see below).

55. Claims 13 to 15 are directed to use according claims 1-12 for the treatment of B lymphocytes. The role of TACI related substances in the treatment of B lymphocytes is disclosed in **D1** (e.g. page 24 at lines 27-30 where the use of chimeric TACI proteins to specifically target B cells is disclosed and page 57 at lines 23-25 which discloses use of antibodies specific to TACI in the treatment of B cell tumors). Accordingly, claims 13 to 15 are anticipated by **D1** despite the fact that it is not clear from the Opposed Patent what "treatment of B lymphocytes" means (see the section on insufficiency below).

56. Claim 16 concerns uses of compounds including TACI related substances for inhibiting antibody production. **D1** discloses use of the TACI receptor for specifically regulating B cell responses particularly where an increase or decrease in antibody production is desired. Therefore, claim 16 is anticipated by **D1**. To the extent that any aspect of claims 13 to 16 is not disclosed by **D1**, these claims lack inventive step over **D1** (see below).

57. Claim 22 is directed to use according to claims 1-21 for inhibiting effector T cells. **D1** discloses that TACI and related molecules activate some populations of T cells and that inhibiting the function of the TACI receptor can be used to treat T cell cancers (see, for example, page 4 at lines 5-12). Claim 22 is therefore anticipated by **D1**. Claims 23 and 24 cover uses according to claim 22 for the biological activities of moderating immune response and effecting immunosuppression respectively. **D1** discloses the use of TACI related substances covered by the claims for suppressing the immune system (see, for example, page 8 at lines 1-5). Claims 23 and 24 are therefore anticipated by **D1**. To the extent that any aspect of claims 22 to 24 is not disclosed by **D1**, these claims lack inventive step over **D1** (see below).

58. Claims 17 to 21 and 25, 27 and 28 are also formulated in "Swiss style", being directed towards specific diseases of the immune system. However, use of TACI related substances in the treatment of such disorders is

disclosed in **D1**. Claim 17 concerns the use according to claim 16 of substances including TACI related substances disclosed in **D1** where the antibody production is associated with autoimmune disease. Use of such substances to treat autoimmune disease is disclosed in **D1** (e.g. page 3 line 34 to page 4 line 3, page 8 at lines 1–6, page 16 at lines 24-28, and page 58 at lines 8-9). **D1** therefore anticipates claim 17.

59. Claim 18 concerns the use according to claim 17 of substances including TACI related substances disclosed in **D1** where the autoimmune disease is SLE, myasthenia gravis, multiple sclerosis, or RA. Uses of such substances for treatment of RA, SLE and myasthenia gravis are disclosed in **D1** (e.g. page 3 line 34 to page 4 line 3 and page 58 at lines 8-18). Claim 18 is therefore anticipated by **D1**.

60. Claim 19 concerns the use according to claims 1 to 18 of substances including TACI related substances disclosed in **D1** for treatment of asthma, bronchitis, emphysema and end stage renal failure, and claim 20 concerns the use according to claim 19 of such substances where the renal disease is glomerulonephritis, vasculitis, nephritis or pyelonephritis. **D1** discloses use of such substances for treating glomerulonephritis and vasculitis (e.g. page 3 line 34 to page 4 line 3 and page 58 at lines 8-18), and therefore anticipates claims 19 and 20.

61. Claim 21 concerns the use according to claims 1 to 20 of substances including TACI related substances disclosed in **D1** for treatment of renal neoplasms, multiple myelomas, lymphomas, light chain neuropathy or amyloidosis. The use of such substances for treatment of myelomas and lymphomas is disclosed in **D1** (e.g. page 16 line 28 to page 17 line 2, page 49 at lines 28-30, page 56 at lines 22-27, page 57 at lines 23-25, and page 58 at lines 20-22). **D1** therefore anticipates claim 21.

62. Claim 25 concerns the use of substances including TACI related substances disclosed in **D1** according to claim 24 referred to above where the

immunosuppression is associated with graft rejection, graft versus host disease, autoimmune disease or inflammation. The use of such substances to treat and/or prevent autoimmune disease, graft-rejection or graft/host disease and in connection with organ transplantation is disclosed in **D1** (e.g. page 8 at lines 1–6 and page 49 at lines 30-32). **D1** therefore anticipates claim 25.

63. Claim 27 concerns the use of substances including TACI related substances disclosed in **D1** according to claims 1-26 referred to above for treatment of inflammation. Claim 28 concerns the use of substances including TACI related substances disclosed in **D1** according to claim 27 where the inflammation is associated with joint pain, swelling, anemia or septic shock. The use of such substances to treat inflammatory diseases, including haemolytic anemia and RA (a key symptom of which is joint pain) is disclosed in **D1** (e.g. page 58 at lines 8-18). **D1** therefore anticipates claims 27 and 28. To the extent that any aspect of claims 17 to 21 and 25 to 28 is not disclosed by **D1**, these claims lack inventive step over **D1** (see below).

64. Claims 36 to 38 of the Opposed Patent cover pharmaceutical compositions including compositions made from antibodies or antibody fragments specific to TACI (SEQ ID NO:6), antibodies and antibody fragments specific to fragments comprising the consensus cysteine-rich pseudo repeat, SEQ ID NO:10 and antibodies and antibody fragments specific to the BR43x2 (SEQ ID NO:2) and its fragment SEQ ID NO:4. Claim 36 covers substances including pharmaceutical compositions comprising such antibodies or antibody fragments and a pharmaceutically acceptable carrier. However, antibodies and antibody fragments specific to TACI are disclosed in **D1** (e.g. page 9 at lines 5-10 and page 49 line 21 to page 52 line 16), as are the two cysteine-rich conserved regions as noted above, and administration of such antibodies as components of therapeutic compositions is also disclosed (e.g. page 58 lines 24-28). Additionally because TACI and BR43x2 share long stretches of amino acids in common.

many antibodies that specifically bind TACI are also likely to bind BR43x2 and BR43x2 fragments. **D1** therefore anticipates claim 36.

65. Claim 37 covers compositions according to claim 36 where the antibody or antibody fragment is selected from the group consisting of (a) polyclonal antibody; (b) murine monoclonal antibody; (c) humanized antibody derived from (b), and, (d) human monoclonal antibody. **D1** discloses all of these antibody types specific to TACI (e.g. page 9 at lines 8-9, page 50 at lines 3-4, page 50 at lines 12-15, and page 50 line 24 to page 51 line 8). Claim 37 is therefore anticipated by **D1**.

66. Claim 38 covers compositions according to claims 36 and 37 where the antibody fragment is selected from the group consisting of F(ab'), Fab, Fv and scFv. TACI-specific antibody fragments such as F(ab') and Fab and means of their preparation are disclosed in **D1** (e.g. page 51 at lines 18-23). Claim 38 is therefore anticipated by **D1**. To the extent that any aspect of claims 36-38 is not disclosed by **D1**, these claims lack inventive step over **D1** (see below).

67. In light of the above, claims 1 to 25, 27, 28 and 36 to 38 lack novelty under Article 54 EPC over **D1**. To the extent that any aspect of claims 1 to 25, 27, 28 and 36 to 38 is not disclosed by **D1**, these claims lack inventive step over **D1** (see below).

D2 – von Bulow et al.

68. **D2** is an article entitled "NF-AT Activation Induced by a CAML-Interacting Member of the Tumor Necrosis Factor Receptor Superfamily" that was published in Science on 3 October 1997. **D2** is therefore prior art under Articles 54(2) and 56 EPC and available as a reference for assessing both the novelty and inventive step of the alleged invention(s) claimed in the Opposed Patent. The authors of **D2** are also the

named inventors of **D1** and, like **D1**, **D2** concerns TACI and related molecules and is cited as a reference in the Opposed Patent.

69. **D2** describes human TACI and provides its amino acid sequence (Fig 1A) which is 100% identical to the human TACI protein which is 'SEQ ID NO:6' in the Opposed Patent (page 40-41)[2]. **D2** therefore disclosed the full-length amino acid sequence of human TACI. **D2** also discloses the location of the two cysteine-rich repeats in TACI (page 138 and Fig 1A). These regions, amino acid residues 33-66 and 70-104 of the sequence in Fig 1A, both fall within the definition of SEQ ID NO:10 of the Opposed Patent (pages 45-47). Two sequences corresponding to SEQ ID NO:10 are therefore disclosed in **D2**.

70. **D2** contains a broad teaching, specifically disclosing the production of TACI, TACI fragments (including the extracellular N-terminal domain of TACI) and TACI fusion proteins, production of TACI and TACI fragments using vectors, host cells and recombinant methods, and the production of antibodies specific for TACI. Furthermore, **D2** discloses that TACI is expressed by B cells.

71. As discussed above, claims 1 to 16 and 22 to 24 of the Opposed Patent are drafted in "Swiss style" and cover compositions which include the extracellular domain of TACI and a TACI fragment (amino acid residues 1-166 of SEQ ID NO:6), fusion proteins containing TACI and TACI fragments (e.g. residues 34-66 and 71-104 and 25-104 of SEQ ID NO:6 and the extracellular domain of TACI), antibodies and antibody fragments specific to TACI (SEQ ID NO:6) and antibodies and antibody fragments specific to BR43x2 (SEQ ID NO:2) and its fragment SEQ ID NO:4. They also cover compositions comprising polypeptides of SEQ ID NO:10 (the cysteine-rich pseudo repeat) and antibodies and antibody fragments specific to such polypeptides. However, they do not claim a therapeutic

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[2] See the preceding footnote.

application (T 4/98) but rather they refer to intrinsic biological activities of TACI and related substances. As these claims are not valid medical use claims, the prior disclosure of these relevant substances deprives these claims of novelty.

72. Further, TACI's biological activities are disclosed in **D2**. For instance, the role of TACI and related substances in relation to B lymphocytes is disclosed in **D2** (e.g. on page 138 which reveals that TACI is located on the surface of B lymphocytes, including resting B lymphocytes). Accordingly, the disclosure of the extracellular domain of TACI (e.g. page 138 states that the N-terminal part of the molecule is extracellular and Figure 1A shows that amino acids 1-166 form the extracellular domain), other TACI fragments (e.g. the fragment comprising the 126 C-terminal amino acids of TACI referred to on page 139), TACI fusion proteins (e.g. TACI fused to N-terminal Flag referred to in the legend to Fig. 4), antibodies specific to TACI (e.g. in the summary on page 138) and the sequences of the two cysteine-rich pseudo repeats given in **D2** anticipates claims 1 to 16 and 22 to 24. Additionally, because TACI and BR43x2 share long stretches of amino acids in common, many antibodies that specifically bind TACI are also likely to bind BR43x2 and BR43x2 fragments. To the extent that any aspect of claims 1 to 16 and 22 to 24 is not disclosed by **D2**, these claims lack inventive step over **D2** (see below).

73. Claims 36 and 37 of the Opposed Patent cover pharmaceutical compositions including compositions made from antibodies or antibody fragments specific to TACI (SEQ ID NO:6), antibodies or antibody fragments specific to polypeptides of SEQ ID NO:10 (the cysteine-rich pseudo repeat) and antibodies and antibody fragments specific to BR43x2 (SEQ ID NO:2) and its fragment SEQ ID NO:4. Claim 36 covers substances including pharmaceutical compositions comprising such antibodies or antibody fragments and a pharmaceutically acceptable carrier. However, as noted above, antibodies and antibody fragments specific to TACI are disclosed in **D2**, as is the location of the two cysteine-rich

pseudo repeats. **D2** therefore anticipates claim 36. Additionally, because TACI and BR43x2 share long stretches of amino acids in common, many antibodies that specifically bind TACI are also likely to bind BR43x2 and BR43x2 fragments. **D2** therefore anticipates claim 36.

74. Claim 37 covers compositions according to claim 36 where the antibody or antibody fragment is selected from the group consisting of (a) polyclonal antibody; (b) murine monoclonal antibody; (c) humanized antibody derived from (b), and, (d) human monoclonal antibody. **D2** discloses such antibodies specific to TACI (e.g. page 138 and the legend to Fig 4C on page 140 disclose polyclonal antibodies specific to TACI). Claim 37 is therefore anticipated by **D2**. To the extent that any aspect of claims 36 and 37 is not disclosed by **D2**, these claims lack inventive step over **D2** (see below).

75. In light of the above, claims 1 to 16, 22 to 24, 36 and 37 lack novelty under Article 54 EPC over **D2**. To the extent that any aspect of claims 1 to 16, 22 to 24, 36 and 37 is not disclosed by **D2**, these claims lack inventive step over **D2** (see below).

D3 – Laabi, et al.

76. **D3** is an article entitled "The BCMA gene, preferentially expressed during B lymphoid maturation, is bidirectionally transcribed" that was published in Nucleic Acids Research in April 1994. **D3** is therefore prior art under Articles 54(2) and 56 EPC and available as a reference for assessing both the novelty and inventive step of the alleged invention(s) claimed in the Opposed Patent.

77. **D3** describes human BCMA, a 184 amino acid protein and gives its amino acid sequence (Fig. 3) which is 100% identical to the human BCMA protein sequence which is 'SEQ ID NO:8' in the Opposed Patent (page

44)[3]. **D3** therefore disclosed the full-length amino acid sequence of human BCMA. It also disclosed a polynucleotide encoding it (Fig. 4). The location of the cysteine-rich pseudo repeat in BCMA is (though not specifically referred to by the authors) also evident from the BCMA sequence (Fig. 3). The region from cysteine residue 8 to cysteine residue 21 contains six cysteine residues and falls within SEQ ID NO:10 of the Opposed Patent (pages 45-47). A sequence corresponding to SEQ ID NO:10 is therefore disclosed in **D3**. **D3** contains a broad teaching, specifically disclosing that BCMA is preferentially expressed in mature B lymphocytes and has been detected in lymphoid B-cell lines. and suggesting that BCMA plays a role in the B lymphocyte development process. **D3** also discloses antibodies specific to BCMA.

78. As discussed above, claims 1 to 16 and 22 to 24 of the Opposed Patent are drafted in "Swiss style" and cover compositions which include the extracellular domain of BCMA and other BCMA fragments (amino acid residues 8-37 and 1-48 of SEQ ID NO:8), fusion proteins containing BCMA and BCMA fragments (residues 8-37, 41-88, 8-88, 89-150 and 1-48 of SEQ ID NO:8 and the extracellular domain of BCMA), and antibodies and antibody fragments specific to BCMA (SEQ ID NO:8). They also cover compositions comprising polypeptides of SEQ ID NO:10 (the cysteine rich pseudo repeat) and antibodies and antibody fragments specific to such polypeptides. However, they do not claim a therapeutic application (T 4/98) but rather they refer to intrinsic biological activities of BCMA and related substances. As these claims are not valid medical use claims, the prior disclosure of these relevant substances deprives these claims of novelty.

79. Further, BCMA's biological activities are disclosed in **D3**. For instance, the role of BCMA in relation to B lymphocytes is disclosed in **D3** (e.g. in

[3] There are some discrepancies in the Opposed Patent regarding the sequence number for the BCMA sequence. For instance, page 3 at line 53 suggests that SEQ ID NO:6 is BCMA

the abstract where the BCMA gene is reported to be preferentially expressed in B lymphocytes suggesting a role for the gene in the B lymphocyte development process). Accordingly, the disclosure of BCMA (e.g. Fig. 3), antibodies specific to BCMA (e.g. in the conclusions at the end of page 1153 the authors note such antibodies have been obtained) and the BCMA sequence which includes the sequence of the cysteine-rich region in **D3** anticipates claims 1 to 16 and 22 to 24.

80. As noted above, claim 36 of the Opposed Patent covers pharmaceutical compositions including compositions made from antibodies or antibody fragments specific to BCMA (SEQ ID NO:8) or from antibodies or antibody fragments specific to the consensus polypeptide of SEQ ID NO:10 and a pharmaceutically acceptable carrier. However, as noted above, antibodies specific to BCMA (a region in the sequence of which falls within SEQ ID NO:10) are disclosed in **D3**. **D3** therefore anticipates claim 36.

81. In light of the above, claims 1 to 16, 22 to 24 and 36 lack novelty under Article 54 EPC over **D3**. To the extent that any aspect of claims 1 to 16, 22 to 24 and 36 is not disclosed by **D3**, these claims lack inventive step over **D3** (see below).

D4 – Gras et al.

82. **D4** is an article entitled "BCMAp: an integral membrane protein in the Golgi apparatus of human mature B lymphocytes" that was published in International Immunology in July 1995. **D4** is therefore prior art under Articles 54(2) and 56 EPC and available as a reference for assessing both the novelty and inventive step of the alleged invention(s) claimed in the Opposed Patent. **D4** shares several of the same authors as **D3** and originates from the same laboratories. It also concerns BCMA.

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whilst page 6 at line 50 suggests it is SEQ ID NO:8. However the amino acid sequence for

83. **D4** describes human BCMA. It does not specifically set out its amino acid sequence but refers directly to earlier papers, including **D3**, where the sequence (which is 100% identical to the human BCMA protein sequence referred to as 'SEQ ID NO:8' in the Opposed Patent) and polynucleotides encoding it were given. These papers and the referenced sequences are therefore incorporated by reference (T 153/85). As noted above, the BCMA sequence disclosed in the **D3** citation referred to includes a region corresponding to SEQ ID NO:10 as defined in the Opposed Patent. **D4** contains a broad teaching, and specifically discloses that BCMA is expressed in B lymphocytes at the pre-B cell stage with expression increasing with B lymphocyte maturation, that expression of BCMA is linked to differentiation in B lymphocytes and that BCMA plays a role in the intracellular traffic of immunoglobulin. **D4** also discloses antibodies specific to BCMA and a BCMA fusion protein.

84. As discussed above, claims 1 to 16 and 22 to 24 of the Opposed Patent are drafted in "Swiss style" and cover compositions which include the extracellular domain of BCMA and other BCMA fragments (amino acid residues 8-37 and 1-48 of SEQ ID NO:8), fusion proteins containing the BCMA and BCMA fragments (residues 8-37, 41-88, 8-88, 89-150 and 1-48 of SEQ ID NO:8 and the extracellular domain of BCMA), and antibodies and antibody fragments specific to BCMA (SEQ ID NO:8). They also cover compositions comprising polypeptides of SEQ ID NO:10 (the cysteine rich pseudo repeat) and antibodies and antibody fragments specific to such polypeptides. However, they do not claim a therapeutic application (T 4/98) but rather they refer to intrinsic biological activities of TACI, BCMA and similar ztnf4 receptors and related substances. As these claims are not valid medical use claims, the prior disclosure of these relevant substances deprives these claims of novelty.

SEQ ID NO:8 (page 44) is that of human BCMA.

85. Further, BCMA's biological activities are disclosed in **D4**. For instance, the expression in B lymphocytes at the pre-B cell stage with expression increasing with B lymphocyte maturation and BCMA's role in the differentiation stage of B lymphocytes and in the intracellular traffic of immunoglobulin are disclosed in **D4** (e.g. in the abstract). Accordingly, the disclosure of BCMA (by reference to papers, including **D3**, which provide the amino acid sequence of BCMA including its cysteine-rich region), a BCMA fusion protein and method of its preparation (e.g. page 1094 where preparation of a GST-BCMA fusion protein is described), and antibodies specific to BCMA and methods of their preparation (e.g. page 1094) in **D4** anticipates claims 1 to 16 and 22 to 24.

86. As noted above, claim 36 of the Opposed Patent covers pharmaceutical compositions including compositions made from antibodies or antibody fragments specific to BCMA (SEQ ID NO:8) or antibodies or antibody fragments specific to the consensus polypeptide of SEQ ID NO:10 and a pharmaceutically acceptable carrier. However, as noted above, antibodies specific to BCMA (a region in the sequence of which falls within SEQ ID NO:10) are disclosed in **D4**. **D4** therefore anticipates claim 36.

87. Claim 37 covers compositions according to claim 36 where the antibody or antibody fragment is selected from the group consisting of (a) polyclonal antibody; (b) murine monoclonal antibody; (c) humanized antibody derived from (b), and, (d) human monoclonal antibody. **D4** discloses such antibodies specific to BCMA (e.g. page 1094 where the preparation of polyclonal antibodies specific to BCMA is described). Claim 37 is therefore anticipated by **D4**. To the extent that any aspect of claims 36 and 37 is not disclosed by **D4**, these claims lack inventive step over **D4** (see below).

88. In light of the above, claims 1 to 16, 22 to 24, 36 and 37 lack novelty under Article 54 EPC over **D4**. To the extent that any aspect of claims 1 to 16, 22

to 24, 36 and 37 is not disclosed by **D4**, these claims lack inventive step over **D4** (see below).

D5 – Madry et al.

89. **D5** is an article entitled "The characterization of murine BCMA gene defines it as a new member of the tumor necrosis factor receptor superfamily" that was published in International Immunology in November 1998. **D5** is therefore prior art under Articles 54(2) and 56 EPC and available as a reference for assessing both the novelty and inventive step of the alleged invention(s) claimed in the Opposed Patent. **D5** shares several of the same authors with **D4** and **D3** and originates from the same laboratories. It also concerns BCMA.

90. **D5** describes both murine and human BCMA and gives the amino acid sequences for both (Fig. 2). The human BCMA amino acid sequence disclosed in **D5** is 100% identical to the human BCMA protein sequence referred to as 'SEQ ID NO:8' in the Opposed Patent (page 3 at line 53 and Fig 1, page 79)[4]. **D5** therefore discloses the full-length amino acid sequence of human BCMA. It also discloses a polynucleotide encoding it (Fig. 2). The location of the cysteine-rich pseudo repeat in BCMA is also specifically disclosed in **D5** (e.g. Fig. 3 where the 6 cysteine residues in the conserved region are identified). This region (residues 8 to 21) falls within SEQ ID NO:10 of the Opposed Patent (pages 45-47). A sequence corresponding to SEQ ID NO:10 is therefore specifically disclosed in **D5**. **D5** contains a broad teaching, specifically disclosing that BCMA is a TNF superfamily receptor which is likely to play a role in the development and regulation of the immune system, and that it is preferentially expressed in lymphoid organs and B lymphocytes. **D5** also identifies the cytoplasmic, trans-membrane and extracellular regions of BCMA.

[4] See footnote 3.

91. As discussed above, claims 1 to 16 and 22 to 24 of the Opposed Patent are drafted in "Swiss style" and cover compositions which include the extracellular domain of BCMA and other BCMA fragments (amino acid residues 8-37 and 1-48 of SEQ ID NO:8), fusion proteins containing BCMA and BCMA fragments (residues 8-37, 41-88, 8-88, 89-150 and 1-48 of SEQ ID NO:8 and the extracellular domain of BCMA), and antibodies and antibody fragments specific to BCMA (SEQ ID NO:8). They also cover compositions comprising polypeptides of SEQ ID NO:10 (the cystcine rich pseudo repeat) and antibodies and antibody fragments specific to such polypeptides. However, they do not claim a therapeutic application (T 4/98) but rather they refer to intrinsic biological activities of BCMA and related substances. As these claims are not valid medical use claims, the prior disclosure of these relevant substances deprives these claims of novelty.

92. Further, BCMA's biological activities are disclosed in **D5**. For instance, the preferential expression of BCMA in mature B lymphocytes and the likely role of BCMA in regulating immune response are disclosed in **D5** (e.g. pages 1694 and 1701). Accordingly, the disclosure of BCMA (Fig 3) and its extracellular region (e.g. page 1698 where Fig 3 identifies the transmembrane region and the N-terminal region containing conserved cysteines and the latter region is said to be normally found in the extracellular domain of TNF receptor proteins) in **D5** anticipates claims 1 to 16 and 22 to 24.

93. In light of the above, claims 1 to 16 and 22 to 24 lack novelty under Article 54 EPC over **D5**. To the extent that any aspect of claims 1 to 16 and 22 to 24 is not disclosed by **D5**, these claims lack inventive step over **D5** (see below).

D6 – WO 98/18921 (Human Genome Sciences, Inc.)

94. **D6** is an application in the name of the Opponent. It was filed on 25 October 1996 and published on 7 May 1998. **D6** is therefore prior art under Articles 54(2) and 56 EPC and available as a reference for assessing both the novelty and inventive step of the alleged invention(s) claimed in the Opposed Patent.

95. **D6** describes ztnf4 (referred to as Neutrokine-alpha), a 285 amino acid protein and gives its amino acid sequence as 'SEQ ID NO:2' (pages 79-80). As noted above, SEQ ID NO:18 is the "ztnf4 fragment", a polypeptide fragment of the human ztnf4 protein which omits N-terminal residues 1 to 21. Amino acid residues 22 to 285 of SEQ ID NO:2 in **D6** are 100% identical to the sequence given for 'SEQ ID NO:18' in the Opposed Patent (pages 51-52)

96. **D6** was the first disclosure of the full length amino acid sequence of ztnf4 as well as a polynucleotide encoding it. **D6** contains a broad teaching, specifically disclosing the production of ztnf4 and ztnf4 polypeptides using vectors, host cells and recombinant methods as well as describing screening methods for identifying agonists and antagonists of ztnf4 activity (including antibodies specific for ztnf4). Furthermore, **D6** describes methods for detecting immune system related disorders and pharmaceutical compositions comprising ztnf4-related substances (including antibodies) for their treatment.

97. As discussed above, claims 3 to 16 and 22 to 24 of the Opposed Patent are drafted in "Swiss style" and cover compositions which include antibodies or antibody fragments specific to the ztnf4 fragment. However, they do not claim a therapeutic application (T 4/98) but rather they refer to intrinsic biological activities of ztnf4 related substances. As these claims are not valid medical use claims, the prior disclosure of these relevant substances deprives these claims of novelty. Accordingly, since **D6** specifically

discloses the ztnf4 fragment (e.g. page 30 line 27), antibodies and antibody fragments specific to ztnf4 polypeptides and methods of preparing such antibodies and antibody fragments (e.g. page 45 line 26 to page 48 line 12), claims 3-16 and 22 to 24 are anticipated by **D6**.

98. Moreover, even if these biologically defined claims were acceptable as proper medical use claims, they would still lack novelty based on **D6**. For instance, **D6** discloses that ztnf4 is a cytokine that plays roles in processes that include cytotoxicity, necrosis, apoptosis, co-stimulation, proliferation, lymph node formation, immunoglobulin class switch and differentiation (page 14 at lines 19-23) and that it is linked to disorders including immunodeficiencies, septic shock, inflammation, graft-host rejection and RA amongst others (page 12 at lines 12-25). The role of ztnf4 in binding to its receptors (now known to include TACI, BCMA and BR43x2) is disclosed in **D6** along with means of identifying its receptors (e.g. page 54 at lines 2-18). **D6** also discloses the use of antagonists (such as antibodies to ztnf4 polypeptides) in conjunction with ztnf4 and its receptor (e.g. page 55 at lines 9-18), their use to prevent the action of ztnf4 by excluding ztnf4 from binding (e.g. page 55 at lines 9-23), and the use of antibodies to inhibit ztnf4 activity in pharmaceutical compositions (e.g. page 57 at lines 24-28). Claim 3 of the Opposed Patent is therefore anticipated.

99. Claims 4-12 cover uses of fusion proteins which are ultimately dependent on claims 1-3. **D6** discloses fusion proteins comprising ztnf4 polypeptides and other polypeptides, and means for their production (e.g. page 27 line 20 to page 28 line 16 and page 41 line 19 to page 42 line 2). Insofar as claims 4-12 cover fusion proteins containing the ztnf4 fragment, the claims are therefore anticipated by **D6**. To the extent that any aspect of claims 3-12 is not disclosed by **D6**, these claims lack inventive step over **D6** (see below).

100. Claims 13 to 15 cover uses of substances including antibodies or antibody fragments specific to the ztnf4 fragment in the treatment of B lymphocytes.

The use of ztnf4 antagonists (such as the claimed antibodies and antibody fragments) to treat B lymphocytes is disclosed in **D6** (e.g. page 56 at lines 15-17). Claims 13 to 15 are therefore anticipated despite the fact that it is not clear from the Opposed Patent what "treatment of B lymphocytes" means (see the section on insufficiency below). To the extent that any aspect of claims 13 to 15 is not disclosed by **D6**, these claims lack inventive step over **D6** (see below).

101. Claim 22 covers use of compounds including antibodies or antibody fragments specific to the ztnf4 fragment for inhibiting effector T cells. **D6** discloses the use of ztnf4 antagonists (such as the claimed antibodies and antibody fragments) for inhibiting T cells (e.g. page 56 at lines 15-17). Claim 22 is therefore anticipated by **D6**. Claims 23 and 24 cover uses according to claim 22 for the biological activities of moderating immune response and effecting immunosuppression respectively. As noted above, **D6** discloses the use of ztnf4 antagonists in the treatment of autoimmune diseases and chronic inflammatory diseases. Claims 23 and 24 are therefore anticipated by **D6**. To the extent that any aspect of claims 22 to 24 is not disclosed by **D6**, these claims lack inventive step over **D6** (see below).

102. Claims 17 to 19, 21 and 25 to 28 are also formulated in "Swiss style", being directed to specific diseases of the immune system. However, such uses of antibodies or antibody fragments specific to ztnf4 polypeptides such as the ztnf4 fragment are disclosed in **D6**. Claim 17 concerns the use according to claim 16 of substances including such antibodies where the antibody production is associated with autoimmune disease. Treatment of autoimmune disease using ztnf4 antagonists (such as the claimed antibodies and antibody fragments) is disclosed in **D6** (e.g. page 56 at lines 15-18). **D6** therefore anticipates claim 17.

103. Claim 18 concerns the use according to claim 17 of substances including antibodies or antibody fragments specific to the ztnf4 fragment where the

autoimmune disease is SLE, myasthenia gravis, multiple sclerosis, or RA. Uses of ztnf4 antagonists (such as the claimed antibodies and antibody fragments) for treatment of such conditions are disclosed in **D6** (e.g. multiple sclerosis on page 56 at lines 19-20 and RA on page 8 at lines 8-11 and page 57 at line 9-11). Claim 18 is therefore anticipated by **D6**.

104. Claim 19 concerns the use according to claims 1 to 18 of substances including antibodies or antibody fragments specific to the ztnf4 fragment for treatment of asthma, bronchitis, emphysema and end stage renal failure. **D6** discloses use of ztnf4 antagonists (such as the claimed antibodies and antibody fragments) for treating such conditions (e.g. asthma on page 57 at lines 3-4 and 19-23), and therefore anticipates claim 19.

105. Claim 21 concerns the use according to claims 1 to 20 of substances including antibodies or antibody fragments specific to the ztnf4 fragment for treatment of renal neoplasms, multiple myelomas, lymphomas, light chain neuropathy or amyloidosis. The use of ztnf4-related substances for such treatments is disclosed in **D6** (e.g., for treating tumors on page 44 at lines 5-7 or for treating lymphocytic leukemias on page 49 at lines 25-27). **D6** therefore anticipates claim 21.

106. Claim 25 concerns the use of substances including antibodies or antibody fragments specific to the ztnf4 fragment according to claim 24 referred to above where the immunosuppression is associated with graft rejection, graft versus host disease, autoimmune disease or inflammation. The use of ztnf4 antagonists (such as the claimed antibodies and antibody fragments) to treat such conditions is disclosed in **D6** (e.g. autoimmune disease and inflammation on page 56 at lines 15-19, and page 57 at lines 4-6 and 15-16). **D6** therefore anticipates claim 25.

107. Claim 26 concerns the use of substances including antibodies or antibody fragments specific to the ztnf4 fragment according to claim 17 referred to above where the autoimmune disease is insulin dependent diabetes mellitus

or Crohn's Disease. The use of ztnf4 antagonists (such as the claimed antibodies and antibody fragments) to treat such conditions is disclosed in **D6** (e.g. insulin dependent diabetes on page 56 at lines 19-20). **D6** therefore anticipates claim 26.

108. Claim 27 concerns the use of substances including antibodies or antibody fragments specific to the ztnf4 fragment according to claims 1 to 26 referred to above for treatment of inflammation. Claim 28 concerns the use of substances including such antibodies according to claim 27 where the inflammation is associated with joint pain, swelling, anemia or septic shock. The use of ztnf4 antagonists (such as the claimed antibodies and antibody fragments) to treat inflammatory diseases, including anemia and RA and associated joint problems is disclosed in **D6** (e.g. page 12 lines 8-11 and page 57 at lines 9-11 and 18-19). **D6** therefore anticipates claims 27 and 28. To the extent that any aspect of claims 17 to 19, 21 and 25 to 28 is not disclosed by **D6**, these claims lack inventive step over **D6** (see below).

109. In light of the above, claims 3 to 19 and 21 to 28 lack novelty under Article 54 EPC over **D6**. To the extent that any aspect of claims 3 to 19 and 21 to 28 is not disclosed by **D6**, these claims lack inventive step over **D6** (see below).

D7 – EP 0 869 180 A1 (SmithKline Beecham Corp.)

110. **D7** is an application in the name of SmithKline Beecham Corporation. It was filed on 1 April 1998 and published on 7 October 1998. **D7** is therefore prior art under Articles 54(2) and 56 EPC and available as a reference for assessing both the novelty and inventive step of the alleged invention(s) claimed in the Opposed Patent.

111. **D7** describes ztnf4 (referred to as "TL5") and gives its amino acid sequence as 'SEQ ID NO:2' (page 18). Amino acid residues 22 to 285 of

SEQ ID NO:2 in **D7** are 100% identical to the sequence given for 'SEQ ID NO:18' in the Opposed Patent (pages 51-52), the ztnf4 fragment referred to above. Like **D6**, **D7** contains a broad teaching, specifically disclosing the production of ztnf4 and ztnf4 polypeptides, agonists and antagonists of ztnf4 activity (including antibodies specific for ztnf4 polypeptides) and treatment of immune system related disorders using pharmaceutical compositions comprising such substances.

112. As discussed above, claims 3 to 16 and 22 to 24 of the Opposed Patent are drafted in "Swiss style" and cover compositions which include antibodies or antibody fragments specific to the ztnf4 fragment. However, they do not claim a therapeutic application (T 4/98) but rather they refer to intrinsic biological activities of ztnf4 related substances. As these claims are not valid medical use claims, the prior disclosure of these relevant substances deprives these claims of novelty. Accordingly, since **D7** discloses the ztnf4 fragment (e.g. page 5 lines 16-22), and antibodies and antibody fragments specific to ztnf4 polypeptides and methods of preparing them (e.g. page 12 at lines 7-27), claims 3-16 and 22 to 24 are anticipated by **D7**.

113. Moreover, even if these biologically defined claims were acceptable as proper medical use claims, they would still lack novelty based on **D7**. For instance, a number of the disorders that can be treated with ztnf4 related molecules are disclosed (e.g. on page 3 at lines 4-8) and means of treating conditions involving both over and under-production of ztnf4 are described (e.g. page 14 at lines 10 to 46). The role of ztnf4 in binding to its receptors (now known to include TACI, BCMA and BR43x2) is disclosed in **D7** along with means of identifying the receptors (e.g. page 13 at lines 45-52). **D7** also discloses the use of antagonists (such as antibodies to ztnf4 polypeptides) in combination with a pharmaceutically acceptable carrier for inhibiting ztnf4 by blocking the binding of related molecules such as receptors to alleviate abnormal conditions (e.g. page 14 at lines 17-21). Claim 3 of the Opposed Patent is therefore anticipated.

114. Claims 4-12 cover uses of fusion proteins which are ultimately dependent on claims 1-3. **D7** discloses fusion proteins comprising ztnf4 polypeptides and other polypeptides (e.g. page 5 at lines 12-22). Insofar as claims 4-12 cover fusion proteins containing the ztnf4 fragment, the claims are therefore anticipated by **D7**. To the extent that any aspect of claims 3-12 is not disclosed by **D7**, these claims lack inventive step over **D7** (see below).

115. Claims 17, 18, 21 and 25 to 28 are also formulated in "Swiss style", being directed towards specific diseases of the immune system. However, such uses of antibodies or antibody fragments specific to ztnf4 polypeptides such as the ztnf4 fragment are disclosed in **D7**. Claim 17 concerns the use according to claim 16 of substances including such antibodies where the antibody production is associated with autoimmune disease. Treatment of autoimmune diseases using ztnf4 antibodies (such as the claimed antibodies and antibody fragments) is disclosed in **D7** (e.g. page 12 at lines 24-25). **D7** therefore anticipates claim 17.

116. Claim 18 concerns the use according to claim 17 of substances including antibodies or antibody fragments specific to the ztnf4 fragment where the autoimmune disease is SLE, myasthenia gravis, multiple sclerosis, or RA. Uses of ztnf4 antibodies (such as the claimed antibodies and antibody fragments) for treatment of such conditions are disclosed in **D7** (e.g. arthritis on page 12 at line 24). Claim 18 is therefore anticipated by **D7**.

117. Claim 21 concerns the use according to claims 1 to 20 of substances including antibodies or antibody fragments specific to the ztnf4 fragment for treatment of renal neoplasms, multiple myelomas, lymphomas, light chain neuropathy or amyloidosis. The use of ztnf4-related substances for such treatments is disclosed in **D7** (e.g. for treating cancers such as lymphoproliferative disorders on page 12 at lines 24-27). **D7** therefore anticipates claim 21.

118. Claim 25 concerns the use of substances including antibodies or antibody fragments specific to the ztnf4 fragment according to claim 24 referred to above where the immunosuppression is associated with graft rejection, graft versus host disease, autoimmune disease or inflammation. The use of ztnf4 antagonists (such as the claimed antibodies and antibody fragments) to treat such conditions is disclosed in **D7** (e.g. for transplant rejection and graft vs. host disease on page 12 at lines 24-27). **D7** therefore anticipates claim 25.

119. Claim 26 concerns the use of substances including antibodies or antibody fragments specific to the ztnf4 fragment according to claim 17 referred to above where the autoimmune disease is insulin dependent diabetes mellitus or Crohn's Disease. Crohn's disease is an inflammatory bowel disease, the general name for diseases that cause inflammation in the intestines. **D7** teaches that anti-ztnf4 antibodies may be used to treat inflammatory bowel disease at page 12 at line 24-27. **D7** therefore anticipates claim 26.

120. Claim 27 concerns the use of substances including antibodies or antibody fragments specific to the ztnf4 fragment according to claims 1-26 referred to above for treatment of inflammation. Claim 28 concerns the use of substances including such antibodies according to claim 27 where the inflammation is associated with joint pain, swelling, anemia or septic shock. The use of ztnf4 antagonists (such as the claimed antibodies and antibody fragments) to treat inflammatory diseases, including arthritis (key symptoms of which are joint pain and swelling) is disclosed in **D7** (e.g. page 12 at line 24). **D7** therefore anticipates claims 27 and 28. To the extent that any aspect of claims 17, 18, 21 and 25 to 28 is not disclosed by **D7**, these claims lack inventive step over **D7** (see below).

121. In light of the above, claims 3 to 18 and 21 to 28 lack novelty under Article 54 EPC over **D7**. To the extent that any aspect of claims 3 to 18 and 21 to 28 is not disclosed by **D7**, these claims lack inventive step over **D7** (see below).

D8 – WO 98/55620 (Regeneron Pharmaceuticals, Inc.)

122. **D8** is an application in the name of Regeneron Pharmaceuticals, Inc. It was filed on 3 June 1998 and published on 10 December 1998. **D8** is therefore prior art under Articles 54(2) and 56 EPC and available as a reference for assessing both the novelty and inventive step of the alleged invention(s) claimed in the Opposed Patent.

123. **D8** describes a fragment of ztnf4 (referred to as HUMAN NTN-2), a 264 amino acid polypeptide and discloses its amino acid sequence (page 16), which is 100% identical to the ztnf4 fragment referred to as 'SEQ ID NO:18' in the Opposed Patent (pages 51 and 52). **D8** therefore disclosed the complete amino acid sequence of the human ztnf4 fragment. It also disclosed a polynucleotide encoding it (page 16). Like **D6** and **D7**, **D8** contains a broad teaching, specifically disclosing the production of the ztnf4 fragment, antibodies specific to the ztnf4 fragment and methods of making and using the ztnf4 fragment and related molecules in compositions for diagnosis and therapy, and in the biopharmaceutical industry.

124. As discussed above, claims 3 to 16 and 22 to 24 of the Opposed Patent are drafted in "Swiss style" and cover compositions which include antibodies or antibody fragments specific to the ztnf4 fragment. However, they do not claim a therapeutic application (T 4/98) but rather they refer to intrinsic biological activities of ztnf4 related substances. As these claims are not valid medical use claims, the prior disclosure of these relevant substances deprives these claims of novelty. Accordingly, the specific disclosure of the ztnf4 fragment (page 16), antibodies and antibody fragments specific to the ztnf4 fragment and methods of preparing such antibodies and antibody fragments (e.g. page 11 line 19 to page 13 line 9 and claim 11) anticipates claims 3 to 16 and 22 to 24. Further, D8 discloses the use of such molecules in pharmaceutical compositions (e.g. claims 14 and 15).

125. In light of the above, claims 3 to 16 and 22 to 24 lack novelty under Article 54 EPC over **D8**. To the extent that any aspect of claims 3 to 16 and 22-24 is not disclosed by **D8**, these claims lack inventive step over **D8** (see below).

(iv) Lack of novelty (Article 54 EPC) assessed at the Later Priority Date

126. Based on the Later Priority Date, in addition to **D1** to **D8**, Schneider et al. (**D9**), Mackay et al. (**D10**) and Moore et al. (**D11**) are available for novelty purposes in respect of at least claims 1, 3 to 7, 10 to 12, 15, 18 to 22, 25 to 28 and 36. The contents of the US patents **D12** to **D17** referred to above are also available for novelty since those applications were filed before the Later Priority date and were subsequently used to claim priority for PCT applications which formed the basis of European Patent applications as described above. In respect of **D12** to **D17**, the Opponent has referred to the original priority filings, it being understood that the same disclosure is included (in addition to other material) in the corresponding PCT applications as filed.

D9 – Schneider et al.

127. **D9** is an article entitled "BAFF, a Novel Ligand of the Tumour Necrosis Factor Family, Stimulates B Cell Growth" that was published in the Journal of Experimental Medicine on 7 June 1999. **D9** is cited as a reference in the Opposed Patent.

128. **D9** describes human and murine ztnf4 (referred to as "BAFF") and gives their amino acid sequences in Fig. 1A (page 1749). The sequence of amino acid residues 22 to 285 of the human ztnf4 sequence is 100% identical to the sequence given for 'SEQ ID NO:18' in the Opposed Patent (pages 51-52), the ztnf4 fragment referred to above. **D9** also discloses experimental data which suggests that ztnf4 plays an important role as a co-stimulator of B cell proliferation and function. In addition, **D9** discloses that the ztnf4

receptor is expressed on B cells as well as disclosing and describing methods of making ztnf4 fragments, fusion proteins and antibodies specific to ztnf4.

129. As discussed above, claims 3 to 16 and 22 to 24 of the Opposed Patent are drafted in "Swiss style" and cover compositions which include antibodies or antibody fragments specific to the ztnf4 fragment. However, they do not claim a therapeutic application (T 4/98) but rather they refer to intrinsic biological activities of ztnf4 related substances. As these claims are not valid medical use claims, the prior disclosure of these relevant substances deprives these claims of novelty. Accordingly, since **D9** discloses the sequence of ztnf4 which includes the sequence of the ztnf4 fragment (Fig 1A, page 1749), antibodies and antibody fragments specific to ztnf4 and methods of preparing them (e.g. page 1749) and ztnf4 fusion proteins (e.g. the Flag-tagged short soluble hBAFF referred to on page 1749), claims 3-16 and 22 to 24 are anticipated by **D9**.

130. Moreover, even if these biologically defined claims were acceptable as proper medical use claims, they would still lack novelty based on **D9**. For instance, the co-stimulatory effect of ztnf4 on immunoglobulin (Ig) production is disclosed as is the role of ztnf4 in T cell and/or dendritic cell-induced B cell growth and potential maturation (e.g. on page 1754). The role of ztnf4 in binding to its receptors (now known to include TACI, BCMA and BR43x2) is disclosed in **D9** along with the fact that expression of the receptor occurs on B cells (e.g. page 1751). Claim 3 of the Opposed Patent is therefore anticipated.

131. Claims 4-12 cover uses of fusion proteins which are ultimately dependent on claims 1-3. **D9** discloses fusion proteins comprising ztnf4 polypeptides and other polypeptides (e.g. page 1749 referred to above). Insofar as claims 4-12 cover fusion proteins containing the ztnf4 fragment, the claims are therefore anticipated by **D9**. To the extent that any aspect of claims 3-

12 is not disclosed by **D9**, these claims lack inventive step over **D9** (see below).

132. In light of the above, claims 3 to 16 and 22 to 24 lack novelty under Article 54 EPC over **D9**. To the extent that any aspect of 3 to 16 and 22 to 24 is not disclosed by **D9**, these claims lack inventive step over **D9** (see below).

D10 – Mackay et al.

133. **D10** is an article entitled "Mice Transgenic for BAFF Develop Lymphocytic Disorders Along with Autoimmune Manifestations" that was published in the Journal of Experimental Medicine on 6 December 1999.

134. **D10** describes experiments conducted involving murine ztnf4 (referred to as "BAFF") produced from a PCR fragment generated by reverse transcription-PCR using the sequence information from **D10**. Although the sequence of human ztnf4 is not expressly set out within **D10**, **D10** refers directly to **D9** which it cites as reference (23) in relation to the sequence of murine ztnf4. **D10** therefore also incorporates the human ztnf4 sequence (and hence 'SEQ ID NO:18' of the Opposed Patent which forms a part of it) by reference (T 153/85), since both sequences are present in the same figure in **D9** (Fig 1A). Other ztnf4 related disclosures in **D9** are also incorporated by reference. **D10**'s broad teaching also includes the disclosure of ztnf4's role as a co-stimulator of B cell proliferation and function and **D10** links ztnf4 over production with various disorders of the immune system.

135. As discussed above, claims 3 to 16 and 22 to 24 of the Opposed Patent are drafted in "Swiss style" and cover compositions which include antibodies or antibody fragments specific to the ztnf4 fragment. However, they do not claim a therapeutic application (T 4/98) but rather they refer to intrinsic biological activities of ztnf4 related substances. As these claims are not valid medical use claims, the prior disclosure of these relevant substances

deprives these claims of novelty. Accordingly, since **D10** incorporates by reference the disclosures of **D9** referred to above, claims 3 to 16 and 22 to 24 are anticipated by **D10**.

136. Moreover, even if these biologically defined claims were acceptable as proper medical use claims, they would still lack novelty based on **D10**. For instance, the co-stimulatory effect of ztnf4 on B cell growth in conjunction with B cell receptor activation is disclosed in **D10** (e.g. on page 1706), as is the fact that ztnf4 induces the proliferation and survival of B cells (e.g. page 1708). Claim 3 of the Opposed Patent is therefore anticipated.

137. Claims 4 to 12 cover uses of fusion proteins which are ultimately dependent on claims 1-3. **D10** discloses fusion proteins comprising murine ztnf4 polypeptides and other polypeptides (e.g. page 1699 where mouse soluble Flag-tagged ztnf4 is disclosed) and also incorporates by reference fusion proteins disclosed in **D9** referred to above. Insofar as claims 4 to 12 cover fusion proteins containing the ztnf4 fragment, the claims are therefore anticipated by **D10**. To the extent that any aspect of claims 3 to 12 is not disclosed by **D10**, these claims lack inventive step over **D10** (see below).

138. Claims 16 to 20 are also formulated in "Swiss style", being directed towards specific diseases of the immune system. Claim 17 concerns the use according to claim 16 of substances including antibodies or antibody fragments specific to the ztnf4 fragment where the antibody production is associated with autoimmune disease. **D10** discloses that over expression of ztnf4 leads to the emergence of autoimmune manifestations and gives examples of such manifestations (e.g. page 1706). **D10** therefore anticipates claim 17.

139. Claim 18 concerns the use according to claim 17 of substances including antibodies or antibody fragments specific to the ztnf4 fragment where the autoimmune disease is SLE, myasthenia gravis, multiple sclerosis, or RA.

D10 discloses that over expression of ztnf4 led to conditions such as SLE and RA in murine models (e.g. pages 1075, 1708 and 1709). Claim 18 is therefore anticipated by **D10**.

140. Claim 19 covers the use of substances including antibodies or antibody fragments specific to the ztnf4 fragment for treatment of asthma, bronchitis, emphysema and end stage renal failure, and claim 20 covers uses according to claim 19 where the renal disease is glomerulonephritis, vasculitis, nephritis or pyelonephritis. **D10** discloses that over expression of ztnf4 led to a condition reminiscent of lupus-like nephritis in murine models (e.g. page 1075), and nephritis is a disease that can be associated with renal failure. **D10** therefore anticipates claims 19 and 20. To the extent that any aspect of claims 16 to 20 is not disclosed by **D10**, these claims lack inventive step over **D10** (see below).

141. In light of the above, claims 3 to 20 and 22 to 24 lack novelty under Article 54 EPC over **D10**. To the extent that any aspect of 3 to 20 and 22 to 24 is not disclosed by **D10**, these claims lack inventive step over **D10** (see below).

D11 – Moore et al.

142. **D11** is an article entitled "BLyS: Member of the Tumour Necrosis Factor Family and B Lymphocyte Stimulator" that was published in Science on 9 July 1999. **D11** is cited as a reference in the Opposed Patent.

143. **D11** describes human ztnf4 (referred to as "BLyS") and gives its amino acid sequence in Fig. 1 (page 261). Amino acid residues 22 to 285 of the human sequence are 100% identical to the sequence given for 'SEQ ID NO:18' in the Opposed Patent (pages 51-52), the ztnf4 fragment referred to above. **D11** also discloses that ztnf4 plays an important role as a co-stimulator of B cell proliferation and function, and that the ztnf4 receptor is expressed on B cells. In addition **D11** discloses ztnf4 fusion proteins, and

antibodies specific to ztnf4 and their possible utility in immune system related disorders.

144. As discussed above, claims 3 to 16 and 22 to 24 of the Opposed Patent are drafted in "Swiss style" and cover compositions which include antibodies or antibody fragments specific to the ztnf4 fragment. However, they do not claim a therapeutic application (T 4/98) but rather they refer to intrinsic biological activities of ztnf4 related substances. As these claims are not valid medical use claims, the prior disclosure of these relevant substances deprives these claims of novelty. Accordingly, since **D11** discloses the sequence of ztnf4, which includes the sequence of the ztnf4 fragment, and a method of its preparation (Fig. 1, page 261 and footnote 28, page 263), antibodies specific to ztnf4 (e.g. ztnf4-specific monoclonal antibodies are disclosed on page 260) and ztnf4 fusion proteins (e.g. the Flag-tagged ztnf4 referred to in the legend to Fig 3, page 262), claims 3 to 16 and 22 to 24 are anticipated by **D11**.

145. Moreover, even if these biologically defined claims were acceptable as proper medical use claims, they would still lack novelty based on **D11**. For instance, the effect of ztnf4 inducing B cell proliferation and immunoglobulin secretion is disclosed (e.g. in the summary on page 260), as is the role of ztnf4 in binding to its receptors (now known to include TACI, BCMA and BR43x2) and their location on B cells (e.g. page 261). Claim 3 of the Opposed Patent is therefore anticipated.

146. Claims 4-12 cover uses of fusion proteins which are ultimately dependent on claims 1 to 3. **D11** discloses fusion proteins comprising ztnf4 polypeptides and other polypeptides (e.g. page 262 referred to above). Insofar as claims 4-12 cover fusion proteins containing the ztnf4 fragment, the claims are therefore anticipated by **D11**. To the extent that any aspect of claims 3-12 is not disclosed by **D11**, these claims lack inventive step over **D11** (see below).

147. Claims 13 to 15 cover uses of substances including antibodies or antibody fragments specific to the ztnf4 fragment in the treatment of B lymphocytes. As noted above, ztnf4's role as a B cell stimulator is disclosed in **D11**, as is the use of ztnf4–related antagonists (such as the claimed antibodies and antibody fragments) as therapies to treat B cell disorders (e.g. page 263). Claims 13 to 15 are therefore anticipated despite the fact that it is not clear from the Opposed Patent what "treatment of B lymphocytes" means (see the section on insufficiency below). To the extent that any aspect of claims 13 to 15 is not disclosed by **D11**, these claims lack inventive step over **D11** (see below).

148. Claims 16 and 17 are also formulated in "Swiss style", being directed towards specific diseases of the immune system. Claim 16 covers the use according to claims 1 to 15 of substances including antibodies or antibody fragments specific to the ztnf4 fragment where the medicament is for inhibiting antibody production. Claim 17 concerns the use according to claim 16 of such substances where the antibody production is associated with autoimmune disease. **D11** discloses that ztnf4 induces immunoglobulin production in mice (e.g., Fig 4C) and that ztnf4–related antagonists (such as the claimed antibodies and antibody fragments) may find medical utility in treating B cell disorders associated with autoimmunity (e.g. page 263). **D11** therefore anticipates claims 16 and 17.

149. Claim 21 covers use of substances including antibodies or antibody fragments specific to the ztnf4 fragment for treatment of renal neoplasms, multiple myelomas, lymphomas, light chain neuropathy or amyloidosis. **D11** discloses that ztnf4–related antagonists (such as the claimed antibodies and antibody fragments) may find medical utility in treating B cell disorders associated with neoplasia (e.g. page 263). **D11** therefore anticipates claim 21.

150. In light of the above, claims 3 to 17 and 21 lack novelty under Article 54 EPC over **D11**. To the extent that any aspect of 3 to 17 and 21 is not disclosed by **D11**, these claims lack inventive step over **D11** (see below).

D12 to D17 – US Patent applications 09/302,863, 60/149,378, 60/143,228, 09/255,794, 60/119,906, 60/166,271

151. These US patent applications were filed by Immunex Corp. (09/302,863, **D12**), Biogen Inc. (60/149,378 and 60/143,228, **D13** and **D14** respectively) the Opponent (09/255,794, **D15**) and Amgen Inc. (60/119,906 and 60/166,271, **D16** and **D17** respectively) and formed the basis for PCT applications which were later published and entered the European Phase as European Patent applications as described more fully above and in Annex A. **D12** to **D17** (insofar as they were incorporated into the relevant PCT applications) are therefore prior art under Article 54(3) and available as references for assessing the novelty of the invention(s) claimed in the Opposed Patent.

152. As discussed above, claims 1 to 16 and 22 to 24 of the Opposed Patent are drafted in "Swiss style" and cover compositions which include TACI, BR43x2 and BCMA fragments and fusion proteins, and the cysteine-rich pseudo repeat of SEQ ID NO:10; antibodies and antibody fragments that bind TACI, BCMA, BR43x2, BR43x2 fragments, the cysteine-rich pseudo repeat of SEQ ID NO:10 and the ztnf4 fragment; and related molecules. However, they do not claim a therapeutic application (T 4/98) but rather they refer to intrinsic biological activities of TACI, BR43x2, BCMA and ztnf4 related substances. As these claims are not valid medical use claims, the prior disclosure of these relevant substances deprives these claims of novelty. Further, the relevant biological activities are disclosed in each of **D12** to **D17**. The role and biological activities of TACI and related substances is disclosed in **D12**, whilst **D13** disclosed the role and biological activities of BCMA and each of **D14** to **D17** disclosed the role and biological activities of ztnf4.

153. Accordingly, the disclosure in **D12** of the extracellular domain of TACI (e.g. page 6 at lines 1-3 and page 12, lines 15-16), other TACI fragments (e.g. page 5 lines 31-35), TACI fusion proteins (e.g. the TACI-Fc fusion protein generated in Example 1 on page 12), antibodies and antibody fragments specific to TACI or ztnf4, which is referred to as TACI-L in this application, (e.g. page 9 at lines 4-28) and the sequences of the two cysteine-rich pseudo repeats of TACI (contained within the TACI amino acid sequence, SEQ ID NO:2 shown in Fig 1B) anticipates claims 1 to 16 and 22 to 24. Additionally, because TACI and BR43x2 share long stretches of amino acids in common, many antibodies that specifically bind TACI are likely to also bind BR43x2 and BR43x2 fragments. **D12** also anticipates other claims of the Opposed Patent including claims 17, 18, 25 to 27 and 36 to 38. For example, page 9 line 29 to page 10 line 3 of **D12** discloses that antagonists of the TACI-ztnf4 interaction may be employed to treat various autoimmune diseases including multiple sclerosis and diabetes as well as other disorders including RA, graft rejection and inflammation, and antibodies and antibody fragments specific to TACI or ztnf4 are also disclosed as noted above. These claims therefore lack novelty under Article 54 EPC over **D12**.

154. Similarly, the disclosure in **D13** (which refers to BCMA as BAFF-R and identifies it as a ztnf4 receptor) of the extracellular domain of BCMA (e.g. page 7 at lines 19-29), other BCMA fragments (e.g. page 11 line 18 to page 12 line 12 and page 14 lines 21-25), BCMA fusion proteins (e.g. page 5 at lines 11-14 and in Example 4 on page 19), antibodies and antibody fragments specific to BCMA (e.g. page 12 line 13 to page 14 line 14) and the sequences of the cysteine-rich pseudo repeat of BCMA (contained within the BCMA amino acid sequence, SEQ ID NO:1 shown in Fig 1, lower line) anticipates claims 1 to 16 and 22 to 24. **D13** also anticipates other claims of the Opposed Patent including claims 17, 19, 21, 25, 27 and 36 to 38. For example, page 5 at lines 3-8 of **D13** discloses uses of BCMA in the treatment of disorders including autoimmune diseases, renal

disorders, inflammation, organ transplantation, B-cell lymph-proliferate disorder, and antibodies and antibody fragments specific to BCMA are also disclosed as noted above. These claims therefore lack novelty under Article 54 EPC over **D13**.

155. Similarly, the disclosures in each of **D14** to **D17** (where ztnf4 is referred to as BAFF, Neutrokine-α and AGP-3 in both **D16** and **D17**), of the ztnf4 fragment, antibodies and antibody fragments specific to the ztnf4 fragment and methods of preparing such antibodies and antibody fragments, and the use of such molecules in pharmaceutical compositions anticipate claims 3 to 16 and 22 to 24. **D14** also anticipates other claims of the Opposed Patent including claims 17, 19, 21, 25 and 27 (e.g. page 5 lines 7-13 and claims 53, 75, 77, 91, 92 and 97 of **D14** on pages 52 to 55). These claims therefore lack novelty under Article 54 EPC over **D14**. **D15** also anticipates other claims of the Opposed Patent including claims 17, 18 and 21 to 28 (e.g. page 113 line 21 to page 115 line 18 of **D15**) giving rise to the lack of novelty of these claims under Article 54 EPC over **D15**. Similarly, **D16** anticipates other claims of the Opposed Patent including claims 17 to 21 and 25 to 28 (e.g. page 17 line 23 to page 19 line 22 of **D16**). These claims therefore lack novelty under Article 54 EPC over **D16**. Finally, **D17** also anticipates other claims of the Opposed Patent including claims 17 to 21 and 25 to 28 (e.g. page 20 line 24 to page 22 line 23 of **D17**). These claims therefore lack novelty under Article 54 EPC over **D17**.

(v) Lack of Inventive Step (Article 56 EPC) assessed at the Claimed Priority Date

156. As noted above, the Opponent submits that inventive step should be assessed at the Later Priority Date for at least claims 1, 3 to 7, 10 to 12, 15, 18 to 22, 25 to 28 and 36 (and their dependent claims) of the Opposed Patent. The assessment of inventive step in relation to the remaining claims and to any of claims 1, 3 to 7, 10 to 12, 15, 18 to 22, 25 to 28 and 36 (and their dependent claims) which, contrary to the Opponent's

submission, the Opposition Division finds have valid priority will be made at the claimed priority date. **D1** to **D8** are available for inventive step purposes at the claimed priority date.

157. As noted above, the Opposed Patent is entitled "Soluble Receptor BR43x2 and Methods of using them for Therapy" and the basis of the invention is described as follows:

"The present invention is based in part upon the discovery of a 1192 bp DNA sequence (SEQ ID NO:1) and corresponding polypeptide sequence (SEQ ID NO:2) which is an isoform of the receptor TACI. The isoform has been designated BR43x2" (page 6 at lines 21-23).

158. The Patentee's characterisation of the alleged invention is surprising given that the monopoly claimed extends significantly beyond the BR43x2 isoform. It claims the uses of compositions containing fragments of the known TNF receptors TACI and BCMA, and pharmaceutical compositions containing antibodies and antibody fragments specific to TACI and BCMA. The specification of the Opposed Patent admits that TACI and BCMA compositions belong to the prior art (e.g. by referencing **D1**, **D2** and **D4** in paragraphs [0002] and [0003]). Furthermore, uses of compositions containing antibodies and antibody fragments specific to the ztnf4 fragment also fall within the claims. Again, the specification of the Opposed Patent admits that such compositions belong to the prior art, as evidenced by Patentees' references (e.g. to **D6** in paragraph [0003]). Compositions containing antibodies and antibody fragments to such polypeptide fragments and their uses are also claimed. Indeed, as will be evident from the discussion above, of the 38 claims in the Opposed Patent, claims 1 to 28 and 36 to 38 extend to known TACI, BCMA and ztnf4-related embodiments, and only the remaining 7 claims (29 to 35) are confined to the TACI isoform BR43x2.

159. As noted above, both **D1** and **D2** describe precisely the same protein sequence as the human TACI protein disclosed in the Opposed Patent. They also disclose the location of the two cysteine-rich repeats in TACI, both of which fall within SEQ ID NO:10 of the Opposed Patent (pages 45-47). **D1**'s broad teaching also includes disclosure of TACI's biological activities, the extracellular N-terminal region of TACI and its function in binding its endogenous ligand (now known to be ztnf4), antibodies and antibody fragments specific to TACI, and the therapeutic uses of such substances in immune system-related disorders and pharmaceutical compositions for their treatment. Similar broad teachings about the biological activities and therapeutic uses of TACI and related molecules are included in **D2**.

160. Further, the skilled reader would recognise that the disclosure in **D1** extends to other TACI-like proteins beyond the human TACI sequence disclosed in **D1** as having the amino acid sequence of SEQ ID NO:2. Indeed **D1** explicitly states that its use of the term 'TACI' and related terms are generic and extend to substantially homologous analogues and allelic variations (page 15 line 31 to page 16 line 7). Furthermore, **D1** describes modifications which can be made to the cloned TACI protein gene sequence at the gene or protein level by numerous strategies known in the art, including modifications where the sequence is cleaved at appropriate sites with restriction endonuclease(s), followed by further enzymatic modification if desired, and isolated and ligated *in vitro* (page 35 at lines 3 to 25). As noted above, the TACI isoform, BR43x2, is identical to TACI save for the replacement of one of the cysteine-rich pseudo repeats, amino acid residues 21 to 67, with a single tryptophan residue. Hence, having been presented with the sequence of TACI in **D1** and directed towards modifications that could be made to the TACI sequence, it would have been obvious to the skilled person to produce variants on the sequence such as BR43x2. Having produced the TACI isoform, BR43x2, the skilled reader of **D1** would expect it to have similar biological activities and therapeutic uses to TACI. Thus, if not anticipated, claims 1 to 38 lack

inventive step over **D1** for claiming the obvious variant of TACI, BR43x2, BR43x2 related molecules and their biological activities and therapeutic uses.

161. As noted above, **D3** to **D5** describe precisely the same protein sequence as the human BCMA protein disclosed in the Opposed Patent. They also disclose (and in the case of **D5** specifically identify) a cysteine-rich conserved region in BCMA which falls within SEQ ID NO:10 of the Opposed Patent (pages 45-47). **D3**'s broad teaching also includes disclosure that BCMA is preferentially expressed in mature B lymphocytes and has been detected in lymphoid B-cell lines, and the suggestion that BCMA plays a role in the B lymphocyte development process. Similar disclosures are to be found in **D4** and **D5**. **D3** and **D4** also disclose antibodies specific to BCMA and BCMA fusion proteins. **D5** also identifies BCMA as a member of the TNF receptor superfamily and describes its extracellular, transmembrane and cytoplasmic regions. Thus, if not anticipated, claims 1 to 28 and 36 to 38 lack inventive step over **D3**, **D4** and/or **D5** for claiming BCMA and BCMA related molecules and their biological activities and therapeutic uses that were obvious in light of **D3**, **D4** and/or **D5**.

162. ztnf4 and the ztnf4 fragment referred to in some of the Opposed Patent's claims (SEQ ID NO:18) were specifically disclosed in **D6** and **D7**, and the ztnf4 fragment was also specifically disclosed in **D8** as described above. Additionally, the disclosures of **D6** to **D8** include antibodies and antibody fragments specific to ztnf4 polypeptides (and to the ztnf4 fragment specifically in **D8**) and fusion proteins containing ztnf4 polypeptides (and containing the ztnf4 fragment specifically in **D8**), as well as descriptions of the biological activities and therapeutic applications of these ztnf4-related molecules. Thus, if not anticipated, claims 3 to 28 lack inventive step over **D6**, **D7** and/or **D8** for claiming uses of ztnf4 related molecules that were obvious in light of **D6**, **D7** and/or **D8**. For example, claim 20 covers uses of substances including antibodies and antibody fragments to the ztnf4

fragment according to claim 19 where the renal disease being treated is glomerulonephritis, vasculitis, nephritis or pyelonephritis. It would have been obvious to the skilled reader of **D6**, **D7**, or alternatively **D8**, that such diseases are associated with autoimmune diseases which are specifically disclosed, and therefore would be treatable using such substances.

163. For these reasons, and to the extent that each of claims 1-38 of the Opposed Patent is not derivable from the teaching of the prior art, then the claims must lack inventive step.

(vi) Lack of Inventive Step (Article 56 EPC) assessed at the Later Priority Date

164. Based on the Later Priority Date, in addition to **D1** to **D8**, Schneider et al. (**D9**), Mackay et al. (**D10**) and Moore et al. (**D11**) are available individually or in combination with each other and/or with common general knowledge for inventive step purposes. If, in these circumstances and contrary to the Opponent's primary submission, the Opposition Division were to find that the claims of the Opposed Patent were novel over the prior art, the Opponent submits that to the extent they are not derivable from the teaching of the prior art, then each of the claims must lack inventive step.

E. Insufficiency (Article 100(b) EPC)

165. The Opponent submits that the Opposed Patent does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. If the Opposition Division finds, contrary to the Opponent's submissions, that any of the claims of the Opposed Patent are novel and involve an inventive step, the Opponent submits that the claims are not sufficient.

166. Claims 13 to 15 of the Opposed Patent concern the treatment of B Lymphocytes. However, B lymphocytes are a subset of cells in the body, not a disease. One of skill in the art is not informed by the specification as

to why B lymphocytes need treatment, much less what outcome should be expected upon having "treated B lymphocytes". In the alternative to its arguments that these claimed uses are not novel and/or lack inventive step, the Opponent submits that for these reasons claims 13 to 15 are insufficient.

167. Claim 3 and its dependent claims (claims 4-28) cover uses of substances that include compositions comprising antibodies or antibody fragments which are specific to SEQ ID NO:18 and antibodies or antibody fragments which are specific to SEQ ID NO:20. SEQ ID NOS:18 and 20 are not described in the specification of the Opposed Patent. They are referred to only in the claims and the sequence listing of the Opposed Patent. One reading the Opposed Patent learns only that SEQ ID NO:18 is of human origin and is 264 amino acids in length and that SEQ ID NO:20 is of murine origin and is 249 amino acids in length. In fact, paragraph [0023] of the Opposed Patent erroneously indicates that SEQ ID NO:19 is a nucleotide encoding murine ztnf4. Careful reading of the sequence listing makes it apparent that SEQ ID NO:17 encodes SEQ ID NO:18, and SEQ ID NO:19 encodes SEQ ID NO:20. Thus, from reading the specification one of skill in the art would not know what SEQ ID NO:18 is and would believe that SEQ ID NO:20 was murine ztnf4. By comparing SEQ ID NOS:18 and 20 to sequences in both publicly and commercially available databases, the Opponent was able to identify SEQ ID NO:18 and SEQ ID NO:20 as the sequences of a fragment of human ztnf4 and of murine TACI respectively. The Opponents were only able to identity SEQ ID NO:20 using information that was entered in those databases subsequent to the filing of the Opposed Patent. There is also no teaching about how or why antibodies or antibody fragments against the proteins shown in SEQ ID NOS:18 and 20 should have the claimed uses, or about how they should be prepared. In the alternative to its arguments that the claimed uses of these substances are not novel and/or lack inventive step, the Opponent submits that for these reasons claim 3 and its dependent claims are insufficient.

F. Requests

168. The Opponent requests the revocation of the Opposed Patent in its entirety.

169. In the event that the Opposition Division does not reach the decision to revoke the Opposed Patent on the basis of the written submission of the Opponent, Oral Proceedings in accordance with Article 116 are requested.

Yours faithfully

Penny Gilbert

DR PENNY X GILBERT

Annex A – Timeline

Date	Event	Concerning	Doc
April 1994	Institut de Genetique Moleculaire and Universite Paris VII paper published in Nucleic Acids Research, 1994, Vol. 22, No. 7, pp. 1147-1154 (Laabi et al.)	BCMA	D3
July 1995	Institut de Genetique Moleculaire and Universite Paris VII paper published in International Immunology, 1995, Vol. 7, No. 7, pp. 1093-1106 (Gras et al.)	BCMA	D4
25 October 1996	Human Genome Sciences files PCT application PCT/US96/17957 (later publishes as WO 98/18921)	ztnf4	
3 March 1997	St Jude Children's Research Hospital files US patent application serial no. 08/810,572	TACI	
12 September 1997	Biogen files US patent application serial no. 60/058,786	ztnf4	
3 October 1997	St Jude Children's Research Hospital paper published in Science, 1997, Vol. 278, pp. 138-141 (von Bulow et al.)	TACI	D2
16 December 1997	Schering Corporation files PCT application PCT/US97/23321 (later publishes as WO 98/27114)	ztnf4	
3 March 1998	St Jude Children's Research Hospital files International Application No. PCT/US98/04270	TACI	
1 April 1998	SmithKline Beecham files EP application No. 98302526.3	ztnf4	
7 May 1998	HGS PCT application PCT/US96/17957 publishes as WO 98/18921	ztnf4	D6
3 June 1998	Regeneron files PCT application PCT/US98/11153 (later publishes as WO 98/55620)	the ztnf4 fragment	
August 1998	Institut de Genetique Moleculaire and Universite Paris VII paper published in International Immunology, 1998, Vol. 10, No. 11, pp. 1693-1702 (Madry et al.)	BCMA	D5
4 September 1998	University of Washington files PCT application PCT/US98/18393 (later publishes as WO 99/11791)	ztnf4	
11 September 1998	Biogen files PCT application PCT/US98/19037 (later publishes as WO 99/12964)	ztnf4	

7 October 1998	SmithKline Beecham European application no. 98302526 publishes as EP 0 869 180	ztnf4	**D7**
11 September 1998	St Jude Children's Research Hospital PCT/US98/04270 publishes as WO 98/39361	TACI	**D1**
10 December 1998	Regeneron PCT application PCT/US98/11153 publishes as WO 98/55620	the ztnf4 fragment	**D8**
22 December 1998	Chiron files PCT application PCT/US98/27474 (later publishes as WO 99/33980)	ztnf4	
7 January 1999	Zymogenetics files the priority document for the Opposed Patent (US patent application serial no. 09/226,533)	TACI/BCMA/ BR43x2/ztnf4	**D18**
12 February 1999	Amgen files US patent application serial no. 60/119,906 (later used as priority document for European Patent application no. 00907280.2)	ztnf4	**D16**
23 February 1999	Human Genome Sciences files US patent application serial no. 09/255,794 (later used as priority document for European Patent application no. 00908739.6)	ztnf4	**D15**
18 March 1999	Biogen PCT application PCT/US98/19037 publishes as WO 99/12964	ztnf4	
30 April 1999	Immunex files US patent application serial no. 09/302,863 (later used as priority document for European Patent application no. 00922273.8)	TACI	**D12**
30 April 1999	Biogen files US patent application serial no. 60/143,228 (later used as priority document for European Patent application no. 00909970.6)	ztnf4	**D14**
7 June 1999	University of Lausanne and others' paper published in J. Exp. Med., Vol. 189, No. 11, 7 June 1999 (Schneider et al.)	ztnf4	**D9**
9 July 1999	Human Genome Sciences paper published in Science, Vol. 285, 9 July 1999 (Moore et al.)	ztnf4	**D11**
9 July 1999	Biogen files US provisional application 60/143,228	ztnf4	
17 August 1999	Biogen files US patent application serial no. 60/149,378 (later used as priority document for European Patent application no. 00957502.8)	ztnf4	**D13**

5 October 1999	Glaxo Group files PCT application PCT/99EP/07303 (later publishes as WO 00/39295)	ztnf4	
19 October 1999	St Jude Children's Research Hospital US patent 5,969,102 granted from application No. 08/810,572	TACI	
4 November 1999	US Dept of Health & Human Services files PCT application PCT/99US/25954 (later publishes as WO 00/26244)	ztnf4	
18 November 1999	Amgen files US patent application serial no. 60/166,271 (later used as priority document for European Patent application no. 00907280.2)	ztnf4	**D17**
6 December 1999	Biogen and others paper published in J. Exp. Med., Vol. 190, No. 11, 6 December 1999 (Mackay et al.)	ztnf4	**D10**
7 January 2000	Zymogenetics files PCT application PCT/US00/00396 (later publishes as WO 00/40716 and granted as EP 1 141 274	TACI/BCMA/ BR43x2/ztnf4	**Opposed Patent**

Annex B – Sequence Identification Nos.

SEQ ID NO. in the Opposed Patent	SEQ ID NO. in the Priority Document (D18)	Description
SEQ ID NO:2	SEQ ID NO:2	Amino acid sequence of BR43x2
SEQ ID NO:4	SEQ ID NO:4	Amino acid sequence of the (soluble) extracellular domain of BR43x2
SEQ ID NO:6	SEQ ID NO:5	Amino acid sequence of human TACI
SEQ ID NO:8	SEQ ID NO:6	Amino acid sequence of human BCMA
SEQ ID NO:10	SEQ ID NO:8	Consensus cysteine-rich pseudo repeat shared by TACI, TACI splice variants and BCMA
SEQ ID NO:18	N/A	Fragment containing amino acid residues 22 to 285 of human ztnf4 (omitting N-terminal residues 1-21 of the full sequence)
SEQ ID NO:20	N/A	Amino acid sequence of murine TACI

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EP 1 141 274

Ich (Wir) / I (We) / Je (Nous)[2]

Human Genome Sciences Inc., 14200 Shady Grove Road, Rockville, MD 20850-7464
United States of America

bevollmächtige(n) hiermit / do hereby authorize / autorise (autorisons) par la présente[3]

Penny Xenia Gilbert and Alexander John Diebler Wilson of
Bristows, 3 Lincoln's Inn Fields, London WC2A 3AA, United Kingdom

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Ort/Place/Lieu: Rockville, USA Datum/Date: 7 June 2004

Unterschrift(en) / Signature(s)[5]: James H. Davis
Executive Vice President and General Counsel

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Zugelassene Vertreter, die sich als solche zu erkennen geben, müssen nach Regel 101(1) in Verbindung mit dem Beschluß des Präsidenten des EPA vom 19. Juli 1991 nur in bestimmten Fällen eine unterzeichnete Vollmacht einreichen (Amtsblatt EPA 1991, 421 und 489). Hingegen müssen nach Artikel 134(7) vertretungsberechtigte Rechtsanwälte sowie Angestellte, die für einen Anmelder gemäß Artikel 133(3) Satz 1 handeln und keine zugelassenen Vertreter sind, eine unterzeichnete Vollmacht einreichen.
b) Die Kästchen sind zutreffendenfalls anzukreuzen.

2 Name(n) und Anschrift(en) sowie Staat des Sitzes oder Wohnsitzes des Vollmachtgebers (der Vollmachtgeber) nach Maßgabe der nachstehenden Regel 26(2) c): „Bei natürlichen Personen sind Familienname und Vorname anzugeben, wobei der Familienname vor dem Vornamen zu stehen hat. Bei juristischen Personen und juristischen Personen gemäß dem für sie maßgebenden Recht gleichgestellten Gesellschaften ist die amtliche Bezeichnung anzugeben. Anschriften sind in der Weise anzugeben, daß die üblichen Anforderungen für eine schnelle Postzustellung an die angegebene Anschrift erfüllt sind. Sie müssen in jedem Fall alle maßgeblichen Verwaltungseinheiten, gegebenenfalls bis zur Hausnummer einschließlich, enthalten."

3 Name(n) und Geschäftsanschrift des Vertreters (der Vertreter) nach Maßgabe der in Ziff. 2 wiedergegebenen Regel 26(2) c).

4 Nummer der Anmeldung(en) (falls bekannt) oder des Patents (der Patente) und Bezeichnung(en) der Erfindung(en).

5 Der Widerruf erfaßt nicht eine gegebenenfalls erteilte allgemeine Vollmacht.

6 Übliche Unterschrift des (der) Vollmachtgeber(s). Wird die Vollmacht für eine juristische Person unterzeichnet, so dürfen nur solche Personen unterzeichnen, die nach Gesetz und/oder Satzung der juristischen Person dazu berechtigt sind (Artikel 58, Regel 101 (1)). Es ist ein Hinweis auf die Unterschriftsberechtigung des Unterzeichnenden zu geben, zum Beispiel Geschäftsführer, Prokurist, Handlungsbevollmächtigter; president, director, company secretary; président, directeur, fondé de pouvoir.
Unterzeichnet ein sonstiger Angestellter einer juristischen Person aufgrund einer speziellen Vollmacht der juristischen Person, so ist dies anzugeben, von der speziellen Vollmacht ist eine Kopie, die nicht beglaubigt zu sein braucht, beizufügen. Eine Vollmacht mit der Unterschrift einer nicht zeichnungsberechtigten Person wird als nicht unterzeichnete Vollmacht behandelt.

II. Hinweise

a) Erstreckt sich die Vollmacht auf mehrere Anmeldungen oder Patente, so ist sie in der entsprechenden Stückzahl einzureichen (vgl. Regel 101(1)).

b) Alle Entscheidungen, Ladungen, Bescheide und Mitteilungen werden an den Vertreter übersandt (vgl. Regel 81). Im Fall der Bevollmächtigung von Angestellten im Sinne des Artikels 133(3) werden die genannten Schriftstücke dem Anmelder übersandt.

c) Regel 101(7) bestimmt: „Sofern die Vollmacht nichts anderes bestimmt, erlischt sie gegenüber dem Europäischen Patentamt nicht mit dem Tod des Vollmachtgebers."

d) Im übrigen vgl. die Mitteilung zu Fragen der Vertretung vor dem EPA im Amtsblatt EPA 4/1978, S. 281 ff.

I. Footnotes to text overleaf

1 (a) The use of this form is recommended when authorising representatives before the European Patent Office – professional representatives and legal practitioners under Article 134(7) – and when authorising employees under Article 133(3), first sentence; as regards the second sentence, no implementing regulation has been issued up to the present time.
Professional representatives who identify themselves as such are required under Rule 101(1), in conjunction with the Decision of the President of the EPO of 19 July 1991, to file a signed authorisation only in particular cases (Official Journal EPO 1991, 421 and 489). However, a legal practitioner entitled to act as professional representative in accordance with Article 134(7), or an employee acting for an applicant in accordance with Article 133(3), first sentence, but who is not a professional representative, must file a signed authorisation.
(b) Where applicable place cross in box.

2 Name(s) and address(es) of the party or parties giving the authorisation and the State in which his (their) residence or principal place of business is located, in accordance with Rule 26(2)(c): "Names of natural persons shall be indicated by the person's family name and given name(s), the family name being indicated before given name(s). Names of legal entities, as well as companies considered to be legal entities by reason of the legislation to which they are subject, shall be indicated by their official designations. Addresses shall be indicated in such a way as to satisfy the customary requirements for prompt postal delivery at the indicated address. They shall in any case comprise all the relevant administrative units, including the house number, if any."

3 Name(s) and address of place of business of the representative(s) in accordance with Rule 26(2)(c) (cf. note 2 above).

4 Application No(s). or patent No(s). (if known) and title(s) of the invention(s).

5 The revocation does not extend to any general authorisation which may have been given.

6 Usual signature(s) of person(s) giving the authorisation. Where the authorisation is signed on behalf of a legal person, only such persons as are entitled to sign by law and/or in accordance with the articles of association or equivalent of the legal person may do so (Article 58, Rule 101(1)). An indication is to be given of the signatory's entitlement to sign, eg president, director, company secretary; Geschäftsführer, Prokurist, Handlungsbevollmächtigter; président, directeur, fondé de pouvoir. If any other employee of a legal person signs by virtue of a special authorisation conferred by the legal person, this is to be indicated and a copy of the special authorisation, which need not be certified, is to be supplied.
An authorisation bearing the signature of a person not entitled so to sign will be treated as an unsigned authorisation.

II. Notices

(a) Authorisations covering more than one application or patent are to be filed in the corresponding number of copies (cf. Rule 101(1)).

(b) All decisions, summonses and communications will be sent to the representative (cf. Rule 81). In cases where employees are authorised under Article 133(3), these documents will be sent to the applicant.

(c) Rule 101(7) states: "Subject to any provisions to the contrary contained therein, an authorisation shall not terminate vis-à-vis the European Patent Office upon the death of the person who gave it".

(d) See also Communication on matters concerning representation before the EPO in Official Journal EPO 4/1978, p. 281 ff.

I. Renvois concernant le texte figurant au recto

1 (a) Il est recommandé d'utiliser ce formulaire pour mandater des représentants devant l'Office européen des brevets – mandataires agréés et avocats au sens de l'article 134(7) – ainsi que pour mandater des employés au sens de l'article 133(3), première phrase; il n'a pas encore été arrêté de dispositions d'application relatives à la deuxième phrase.
En vertu de la règle 101(1) en liaison avec la décision du Président de l'OEB en date du 19 juillet 1991, les mandataires agréés qui se font connaître comme tels ne sont tenus que dans certains cas de déposer un pouvoir signé (cf. Journal officiel de l'OEB 1991, 421 et 489). En revanche, les avocats habilités à agir en qualité de mandataires en vertu de l'article 134(7), ainsi que les employés qui agissent pour le compte d'un demandeur conformément à l'article 133(3), 1re phrase, et qui ne sont pas des mandataires agréés, doivent déposer un pouvoir signé.
(b) Faire une croix dans la case si nécessaire.

2 Nom(s) et adresse(s), Etat du siège ou du domicile du (des) mandant(s), dans les conditions prévues à la règle 26(2) c) et reproduites ci-dessous: «Les personnes physiques doivent être désignées par leurs noms et prénoms, les noms précédant les prénoms. Les personnes morales et les sociétés assimilées aux personnes morales en vertu de la législation qui les régit doivent figurer sous leur désignation officielle. Les adresses doivent être indiquées selon les exigences usuelles en vue d'une distribution postale rapide à l'adresse indiquée. Elles doivent en tout état de cause comporter toutes les indications administratives pertinentes, y compris, le cas échéant, le numéro de la maison.»

3 Nom(s) et adresse professionnelle du (des) mandataire(s), dans les conditions prévues à la règle 26(2) c) et mentionnées à la remarque 2.

4 Numéro de la (des) demande(s) (s'il est connu) ou du (des) brevet(s) et titre(s) de l'invention (des inventions).

5 La révocation ne s'étend pas à un pouvoir général éventuellement donné.

6 Signature(s) habituelle(s) du (des) mandant(s). Lorsque le pouvoir est signé au nom d'une personne morale, seules sont habilitées à signer les personnes auxquelles cette qualité est reconnue en vertu de la loi et/ou du statut de la personne morale concernée (article 58, règle 101 (1)). Il convient d'indiquer la qualité du signataire, par exemple: président, directeur, fondé de pouvoir; Geschäftsführer, Prokurist, Handlungsbevollmächtigter; president, director, company secretary.
Il y a lieu de signaler les cas où un autre employé d'une personne morale signe en vertu d'un pouvoir spécial conféré par la personne morale et de fournir alors une copie, qui peut ne pas être certifiée conforme, de ce pouvoir spécial. Un pouvoir portant la signature d'une personne non habilitée à signer sera considéré comme non signé.

II. Notes

a) Si le pouvoir est donné pour plusieurs demandes ou plusieurs brevets, il doit être fourni un nombre correspondant d'exemplaires (cf. règle 101(1)).

b) Toutes les décisions, citations, notifications seront adressées au mandataire (voir règle 81). Dans le cas où des employés au sens de l'article 133(3) sont mandatés, les pièces mentionnées sont envoyées au demandeur.

c) La règle 101(7) stipule: «Sauf disposition contraire du pouvoir, celui-ci ne prend pas fin, à l'égard de l'Office européen des brevets, au décès du mandant.»

d) Pour le reste, se reporter à la Communication concernant les questions relatives à la représentation près l'OEB, parue au Journal officiel de l'OEB, 4/1978, 281 s.